REVISTA ESPAÑOLA DE Quimioterapia

SPANISH JOURNAL OF CHEMOTHERAPY

ISSN: 0214-3429
Volumen 34
Número 1
Febrero 2021
Páginas: 1-71

Publicación Oficial de la Sociedad Española de Quimioterapia

REVISTA ESPAÑOLA DE
Quimioterapia

Revista Española de Quimioterapia tiene un carácter multidisciplinar y está dirigida a todos aquellos profesionales involucrados en la epidemiología, diagnóstico, clínica y tratamiento de las enfermedades infecciosas

Fundada en 1988 por la Sociedad Española de Quimioterapia

Indexada en
Science Citation Index Expanded (SCI),
Index Medicus (MEDLINE),
Excerpta Medica/EMBASE,
Índice Médico Español (IME),
Índice Bibliográfico en Ciencias de la Salud (IBECS)

Secretaría técnica
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Facultad de Medicina
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revista@seq.es
Disponible en Internet:
www.seq.es

Sociedad Española de Quimioterapia

Publicidad y Suscripciones
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28040 Madrid

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Publicación que cumple los requisitos de soporte válido

ISSN
0214-3429

e-ISSN
1988-9518

Depósito Legal
M-32320-2012

Maquetación
Vic+DreamStudio

Impresión
España

Esta publicación se imprime en papel no ácido.
This publication is printed in acid free paper.

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Quimioterapia

Sumario

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Official journal of the Spanish Society of Chemotherapy

Revisión

Revista Española de Quimioterapia
doi:10.37201/req/110.2020

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Vacuna antigripal trivalente de alta dosis: seguridad e inmunogenicidad

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Article history
Received: 21 September 2020; Revision Requested: 13 October 2020; Revision Received: 15 October 2020; Accepted: 19 October 2020; Published: 19 November 2020

RESUMEN

Las personas mayores son uno de los colectivos que más sufren los efectos de la gripe estacional. Aunque la vacuna antigripal es efectiva a la hora de prevenir la infección por el virus de la gripe y sus complicaciones, no resulta tan efectiva en personas de edad avanzada debido al fenómeno de inmunosenescencia asociado a la edad. Desde 2009 existe en EE. UU. una vacuna antigripal trivalente de alta dosis aprobada para la inmunización de personas ≥ 65 años con una concentración de antígeno cuatro veces mayor que la vacuna estándar. Múltiples ensayos clínicos llevados a cabo a lo largo de distintas temporadas, y mediante diferentes metodologías, han demostrado que la vacuna antigripal trivalente de alta dosis no solo es más efectiva, sino que además presenta un perfil de seguridad similar y es más inmunogénica que la vacuna de dosis estándar en la prevención de la gripe y sus complicaciones en personas de avanzada edad. En este documento se hace una revisión de la evidencia científica actual sobre la seguridad e inmunogenicidad de la vacuna antigripal de alta dosis en personas ≥ 65 años, y se incluye información de ensayos clínicos aleatorizados, estudios observacionales con datos de práctica clínica real y revisiones sistemáticas y metaanálisis.

Palabras clave: vacuna de la gripe; alta dosis; seguridad; inmunogenicidad; ancianos

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High-dose trivalent influenza vaccine: safety and immunogenicity

ABSTRACT

Adults aged 65 years or older suffer the most severe health effects of seasonal flu. Although the influenza vaccine is effective in preventing influenza virus infection and its complications, it is not as effective in the elderly due to age-associated immunosenescence phenomenon. Since 2009, a high-dose trivalent influenza vaccine has been approved in the United States for the immunization of people ≥ 65 years with an antigen concentration four times higher than the standard vaccine. Multiple clinical trials carried out over different seasons, and using different methodologies, have shown that the high-dose trivalent influenza vaccine is not only more effective, but it also has a similar safety profile and is more immunogenic than the standard dose vaccine in the prevention of flu and its complications in the elderly. This document reviews the current scientific evidence on the safety and immunogenicity of high-dose influenza vaccine in people aged 65 years and over, and includes information from randomized clinical trials, observational studies with data from real clinical practice, and systematic reviews, and meta-analysis.

Keywords: Influenza vaccine; High-dose influenza vaccine; Vaccine immunogenicity; Vaccine safety; Elderly population

INTRODUCCIÓN

La gripe afecta a personas de todas las edades y con mayor frecuencia a las poblaciones *naive* de niños y adolescentes, sin embargo el riesgo de sufrir complicaciones graves se sitúa en los extremos de la vida (niños menores de 5 años y ancianos), siendo la mortalidad notablemente más elevada en los de mayor edad y especialmente aquellos con comorbilidades [1-3]. Las tasas de morbilidad, hospitalización y mortalidad asociadas a la gripe en este grupo de riesgo sufren una tendencia

al alza debido al envejecimiento de la población en los países desarrollados [4].

La inmunosenescencia que ocurre a partir de los 65-70 años de vida, hace que la inmunogenicidad de la vacuna de gripe sea distinta y menor, en general, en este grupo de población [5-8]. De hecho, se estima que la respuesta a la vacunación en las personas mayores es entre 2 y 4 veces menos intensa que en las personas más jóvenes [4, 9-12].

Por otra parte, la inmunogenicidad generada por las vacunas de gripe inactivadas es diferente para cada tipo y subtipo de virus incluidos en la vacuna. Existe, además, el fenómeno de la huella serológica de la primoinfección gripal, que condiciona la respuesta a futuras infecciones, y que hace que las personas nacidas antes del año 1957 respondan peor al H3N2, ya que que pudieron primoinfectarse con el subtipo H1N1 [13]. Estos datos ponen de manifiesto la necesidad de formulaciones vacunales más inmunogénicas para personas mayores. La capacidad inmunogénica de las vacunas se basa en unos parámetros definidos por distintos estamentos sanitarios que se resumen en la Tabla 1.

Existen distintas aproximaciones para incrementar la inmunogenicidad de las vacunas antigripales, como el uso de adyuvante o vías de administración alternativas (por ej., intradérmica). Una reciente alternativa para generar mayor inmunogenicidad y efectividad clínica en personas mayores o inmunodeprimidas ha sido la inclusión de cantidades notablemente mayores de antígeno gripal en la vacuna [14].

En 2009, la FDA aprobó de forma acelerada una vacuna antigripal trivalente inactivada de virus fraccionados de alta dosis (IIV3HD, Fluzone High-Dose®, SanofiPasteur, PA, USA) para la inmunización de personas ≥ 65 años de administración por vía intramuscular. Esta vacuna contiene 60 µg de hemaglutinina (HA) por cepa, lo que supone cuatro veces el contenido de cada virus comparado con las vacunas clásicas trivalentes de dosis estándar (IIV3-SD) [15, 16]. La FDA aprobó la vacuna IIV3-HD basándose en estudios que demostraron respuestas mayores de títulos inhibidores de la hemaglutinación (IHA,) en ≥ 65 años, en comparación con la vacuna de dosis estándar, para las cepas A/H1N1 y A/H3N2, y no inferiores para la cepa B [17-19].

Al menos cuatro ensayos clínicos aleatorizados han demostrado en ≥ 65 años que la vacuna IIV3HD es segura, más inmunogénica y más eficaz previniendo la gripe y sus complicaciones que la vacuna trivalente de dosis estándar (IIV3-SD) [14].

En este artículo de revisión se han analizado las publicaciones sobre inmunogenicidad y la seguridad de la vacuna antigripal IIV3-HD, incluyendo información sobre los principales ensayos clínicos aleatorizados realizados en mayores de 65 años con un tamaño muestral de al menos 1900 sujetos, así como estudios observacionales con datos de vida real y las revisiones sistemáticas o metaanálisis de mayor relevancia.

INMUNOGENICIDAD DE LA VACUNA ANTIGRIPAL TRIVALENTE DE ALTA DOSIS

La FDA aprobó unos criterios a cumplir por la nueva vacuna de alta dosis en comparación con la clásica trivalente con respecto a su inmunogenicidad en términos de tasas de seroconversión y razón de los títulos medios geométricos (GMT) para cada cepa viral en el ensayo clínico pivotal de inmunogenicidad (FIM05).

– Para cada cepa, se consideró que la vacuna IIV3HD sería no inferior a la IIV3SD si el límite inferior del intervalo de confianza [IC 95%] del ratio de las GMT postvacunales de IIV3-HD vs IIV3-SD era > 0,67, y se consideraría superior si fuera > 1,5.

– Respecto a las tasas de seroconversión, se consideró superioridad si el límite inferior del intervalo de confianza [IC 95%] para la diferencia en las tasas de seroconversión era ≥ 10%, y no inferioridad si superaba el -10%.

– Se consideró que la vacuna HD tenía una respuesta inmunogénica superior a la SD para el conjunto de todas las cepas incluidas en la vacuna, si se alcanzaba la superioridad para al menos dos cepas y la no inferioridad para la restante.

Ensayos clínicos de inmunogenicidad. Se han realizado diferentes estudios para demostrar la superioridad inmunogénica de la vacuna IIV3HD frente a la SD en personas mayores de 65 años. Los subanálisis de estos ensayos clínicos analizan la res-

Tabla 1 **Criterios de inmunogenicidad para la vacuna IIV3HD frente a la gripe definidos por la FDA y definiciones utilizadas en el texto [18, 32]**

Términos	Definiciones
GMT prevacunal	Media geométrica de los títulos de anticuerpos en una población antes de la vacunación.
GMT postvacunal	Media geométrica de los títulos de anticuerpos en una población después de la vacunación.
Razón de incremento de GMT	Cociente entre la GMT postvacunal y la GMT prevacunal de una vacuna.
GMT ratio	Cociente entre las GMT postvacunales de vacuna IIV3-HD y IIV3-SD.
Tasa de seroconversión	Porcentaje de individuos con títulos HAI postvacunales 4 veces superiores a los prevacunales y superiores o iguales a 1:40.
Tasa de seroprotección	Porcentaje de individuos con títulos HAI ≥ 1:40.

GMT: títulos medios geométricos; HAI: Inhibición de la hemaglutinación media geométrica.

Tabla 2 **Ensayos clínicos en los que se ha analizado la inmunogenicidad de la vacuna IIV3-HD. Se muestran los valores máximos y mínimos para los diferentes parámetros inmunogénicos en las tres cepas (H1N1, H3N2 y B).**

Autor / año	Tipo de estudio	Temporada	Cepa dominante	N		Inmunogenicidad (IIV3-HD vs. IIV3-SD)		
				IIV3-HD	IIV3-SD			
Falsey et al. 2009 [18]	Ensayo clínico fase III	2006-07	A/H1N1	2.576	1.275	Ratio GMT títulos HIA postvacunación (HD/SD) para las tres cepas (A/H1N1, A/H3N2, B)		De 1,3 a 1,8
						Diferencia tasas seroconversión (HD – SD) para las tres cepas		De 11,8% a 25,4%
						Diferencia tasas seroprotección (HD – SD) para las tres cepas		De 2, 8% a 13,1%
						% Sujetos con títulos HIA postvacunación ≥ 1:80 (*P*<0,001 para todos los valores)	A/H1N1	73% (HD) vs.51%(SD)
							A/H3N2	97% vs. 89%
							B	52% vs. 39%
						% Sujetos con títulos HIA postvacunación ≥ 1:160 (*P*<0,001 para todos los valores)	A/H1N1	45% vs. 26%
							A/H3N2	91% vs. 78%
							B	22% vs. 16%
Tsang et al . 2014 [21]	Ensayo clínico de fase II	2007-08	A/H1N1-A/H3N2	320	319	Ratio GMT títulos HIA postvacunación (HD/SD) para las tres cepas		De 1,4 a 2,1
DiazGranados et al. 2013 [24]	Ensayo clínico fase IIIb	2009-10	A/H1N1pdm09	2.000	991	Ratio GMT títulos HIA postvacunación (HD/SD) para las tres cepas		De 1,6% a 1,7%
						Diferencia tasas seroprotección (HD – SD) para las tres cepas		De 2,5% a 8,9%
DiazGranados et al. 2014 [25]	Ensayo clínico fase IIIb/IV (FIM12)	2011-12	A/H3N2	2.375	2.382	Ratio GMT títulos HIA postvacunación (HD/SD) para las tres cepas		1,4 a 2,0
						Diferencia tasas seroprotección (HD – SD) para las tres cepas		De 2,7% a 7,7%
		2012-13	A/H3N2	2.879	2.872	Ratio GMT títulos HIA postvacunación (HD/SD) para las tres cepas		De 1,6 a 1,8
						Diferencia tasas seroprotección (HD – SD) para las tres cepas		De 3,6% a 13,4%

GMT: títulos medios geométricos; HAI: Inhibición de la hemaglutinación media geométrica; HD: alta dosis, SD: dosis estándar

Tabla 3 **Subanálisis de ensayos clínicos aleatorizados en los que se ha analizado la inmunogenicidad de la vacuna IIV3-HD**

Autor / año	Tipo de estudio	Temporada	Cepa dominante	N		Inmunogenicidad (IIV3-HD vs. IIV3-SD)		
DiazGranados et al. 2015 [20]	Subanálisis del ensayo FIM12: inmunogenicidad en función de la edad, la comorbilidad y la fragilidad	2011-12 2012-13	A/H3N2	15.990	15.993	Ratio GMT títulos HIA postvacunación (HD/SD)	A/California/7/2009 (H1N1) (Año 1/Año 2)	65 - 74 años	1,8 (1,7 - 1,9)
							A/Victoria/210/2009 (H3N2) (Año 1)		2,1 (1,9 - 2,3)
							A/Victoria/361/2011 (H3N2) (Año 2)		1,7 (1,6 - 1,9)
							B/Brisbane/60/2008 (Año 1)		1,5 (1,4 - 1,6)
							B/Texas/6/2011 (Año 2)		1,6 (1,5- 1,7)
							A/California/7/2009 (H1N1) (Año 1/Año 2)	≥ 75 años	1,8 (1,6 - 1,9)
							A/Victoria/210/2009 (H3N2) (Año 1)		1,7 (1,5 - 2,0)
							A/Victoria/361/2011 (H3N2) (Año 2)		2,0 (1,8 - 2,2)
							B/Brisbane/60/2008 (Año 1)		1,2 (1,1 - 1,4)
							B/Texas/6/2011 (Año 2)		1,6 (1,5 - 1,8)
							A/California/7/2009 (H1N1) (Año 1/Año 2)	≥ 1 comorbilidad de alto riesgo	1,8 (1,7 - 2,0)
							A/Victoria/210/2009 (H3N2) (Año 1)		2,0 (1,8 - 2,2)
							A/Victoria/361/2011 (H3N2) (Año 2)		1,9 (1,8 - 2,0)
							B/Brisbane/60/2008 (Año 1)		1,4 (1,3 - 1,5)
							B/Texas/6/2011 (Año 2)		1,7 (1,6 - 1,8)
							A/California/7/2009 (H1N1) (Año 1/Año 2)	≥ 3 condiciones de fragilidad	1,8 (1,7 - 2,0)
							A/Victoria/210/2009 (H3N2) (Año 1)		1,9 (1,7 - 2,2)
							A/Victoria/361/2011 (H3N2) (Año 2)		1,9 (1,7 - 2,1)
							B/Brisbane/60/2008 (Año 1)		1,4 (1,2 - 1,5)
							B/Texas/6/2011 (Año 2)		1,6 (1,4 - 1,8)

Tabla 3 **Subanálisis de ensayos clínicos aleatorizados en los que se ha analizado la inmunogenicidad de la vacuna IIV3-HD (cont.)**

Autor / año	Tipo de estudio	Temporada	Cepa dominante	N	Inmunogenicidad (IIV3-HD vs. IIV3-SD)		
DiazGranados et al. 2016 [15]	Subanálisis del ensayo FIM12: inmunogenicidad en función de la vacuna recibida en el año anterior	2011-12 2012-13	A/H3N2	643	Ratio GMT títulos HIA postvacunación (HD/SD)	Año 1 HD Año 2 HD	A/H1N1 1,6 (1,4 - 1,8)
							A/H3N2 1,6 (1,4 - 1,9)
							B 1,5 (1,4 - 1,7)
				605		Año 1 SD Año 2 HD	A/H1N1 2,1 (1,8 - 2,4)
							A/H3N2 1,9 (1,7 - 2,2)
							B 1,6 (1,4 - 1,8)
				1.248		Año 1 HD o SD Año 2 HD	A/H1N1 1,8 (1,6 - 2,1)
							A/H3N2 1,8 (1,6 - 2,0)
							B 1,6 (1,4 - 1,7)
				639		Año 1 HD Año 2 SD	A/H1N1 1,0 (0,9 - 1,2)
							A/H3N2 1,0 (0,9 - 1,1)
							B 0,9 (0,8 - 1,0)

GMT: títulos medios geométricos; HAI: Inhibición de la hemaglutinación media geométrica; HD: alta dosis, SD: dosis estándar

puesta en distintas temporadas y en función de la edad, comorbilidad o fragilidad de los sujetos, así como el tipo de vacuna recibido en la temporada previa (Tabla 2 y Tabla 3). También se han llevado a cabo estudios para analizar la respuesta inmune de la HD frente a otras vacunas de inmunogenicidad potenciada como la intradérmica y la adyuvada [20, 21].

Temporada 2006-07: Un estudio de fase III multicéntrico aleatorizado (FIM05) comparó la inmunogenicidad y la seguridad de la vacuna IIV3HD frente a la vacuna IIV3SD en ≥ 65 años (n = 3.837, de los cuales 1.342 eran mayores de 75 años). Entre los meses de octubre y diciembre de 2006 en EE. UU, recibieron la vacuna de alta dosis un total de 2.576 personas. [18]. El estudio demostró que la inmunogenicidad (Razón de las GMT de la IHA) de la vacuna IIV3HD era superior (el límite inferior del IC 95%>1,5 a los 28 días postvacunación para las cepas A/H1N1 (1,7; IC 95% 1,6-1,8) y A/H3N2 (1,8; IC 95% 1,7-1,8) y la inmunogenicidad fue no inferior y mayor para la cepa B (1,3; IC 95% 1,2-1,4) [18]; además, las GMT y las tasas de seroconversión fueron significativamente más altas para las tres cepas de la vacuna, con diferencias absolutas entre la vacuna IIV3HD y la IIV3SD del 25,4% (IC 95% 22,4-28,5) para la cepa A/H1N1, del 18,4% (IC 95% 15,1-21,7) para la cepa A/H3N2 y del 11,8% (IC 95% 8,6-15,0) para la cepa B [18].

Las tasas de seroprotección fueron más altas en los participantes que recibieron la vacuna IIV3HD que en los que recibieron la vacuna IIV3-SD, frente a todas las cepas (A/H1N1, 90% vs. 77%; A/H3N2, 99% vs. 77% y B, 79% vs. 68%, respectivamente) [18]. Lo mismo sucedió con los títulos HIA postvacunación ≥ 1:80 frente a todas las cepas (A/H1N1, 73% *vs.* 51%; A/H3N2, 97% *vs.* 89% y B, 52% *vs.* 39%, respectivamente; $p < 0,001$) y ≥ 1:160 (A/H1N1, 45% *vs.* 26%; A/H3N2, 91% *vs.* 78% y B, 22% *vs.* 16%, respectivamente; $p < 0,001$) [18].

Se demostró además que la superioridad inmunogénica de la vacuna IIV3HD se mantenía en los ≥ 75 años y en aquellos que presentaban enfermedad cardiopulmonar; dos grupos considerados de alto riesgo de sufrir complicaciones por gripe, que en general responden de forma subóptima a la vacuna antigripal estándar [22, 23]. También se observaron mejores respuestas inmunológicas en participantes con títulos muy bajos de anticuerpos previos a la vacunación (<1:10); GMT IIV3HD *vs.* IIV3SD: 83 *vs.* 45 para la cepa A/H1N1, 283 vs. 124 para la cepa A/H3N2 y 42 vs. 27 para la cepa B ($p < 0,001$ para todas las comparaciones) [18].

Estos resultados demostraron la mayor inmunogenicidad de la vacuna de alta dosis respecto a la de dosis de estándar, según los criterios acordados con la FDA en el protocolo del estudio [18].

Temporada 2007-2008. Un ensayo aleatorizado de fase II llevado a cabo en EE. UU. proporcionó datos adicionales sobre la inmunogenicidad de la vacuna IIV3HD respecto a vacunas experimentales de administración intradérmica (IDIIV3). El ensayo incluyó vacunas que contenían 15 µg (IDIIV315, n = 636) y 21 µg (IDIIV321, n = 634) de antígeno HA por cepa de vacuna trivalente con dosis estándar (n = 319) y la vacuna IIV3HD (n = 320) en adultos ≥ 65 años. Las GMT de títulos HIA a los 28 días postvacunación fueron significativamente más altas con la vacuna IIV3HD que, con cualquiera de las dos vacunas intradérmicas, para las tres cepas [21]. La vacuna de alta dosis es más inmunogénica que la vacuna de administración intradérmica, incluso cuando se aumenta la cantidad de antígeno en esta última [21].

Temporada 2009-10. El estudio de fase IIIb aleatorizado (FIM07) en centros de EE. UU. [24], demostró también que, en ≥ 65 años, tanto las GMT de títulos IHA como las tasas de seroprotección a los 28 días postvacunación, evaluadas en un subgrupo aleatorio de participantes (2.000 vacunados con la vacuna IIV3-HD y 991 con la IIV3-SD), fueron significativamente más altas con la vacuna IIV3-HD que con la vacuna de

dosis estándar para las tres cepas: (i) las ratios de las GMT HIA (IIV3-HD/IIV3-SD) fueron 1,57 (IC 95% 1,44-1,71) para la cepa A/H1N1, 1,74 (IC 95% 1,57-1,94) para la cepa A/H3N2 y 1,61 (IC 95% 1,48-1,75) para la cepa B; (ii) las diferencias de los porcentajes de seroprotección (IIV3-HD – IIV3-SD) fueron 7,6% (IC 95% 5,4-9,9) para la cepa A/H1N1, 2,5% (IC 95% 1,1-4,2) para la cepa A/H3N2 y 8,9% (IC 95% 6,4-11,5) para la cepa B[24].

Temporadas 2011-12 y 2012-13: En el ensayo clínico aleatorizado de fase IIIb/IV FIM12, que se llevó a cabo durante dos temporadas consecutivas y en el que participaron 31.989 sujetos ≥65 años de EE.UU. y Canadá, se observó que las GMT de los títulos HIA las tasas de seroprotección 28 días después de la vacunación fueron significativamente más altas con la vacuna IIV3HD que con la vacuna IIV3SD, para las tres cepas incluidas en la vacuna y en las dos temporadas [25].

– Temporada 2011-12 (año 1): Tal y como se muestra en la Tabla 2, la ratio GMT (IIV3HD/IIV3SD) fue >1 para las cepas A/H1N1, A/H3N2 y B. La diferencia en el porcentaje de seroprotección (IIV3HD - IIV3SD) fue de 3,9, 2,7 y 7,7 puntos porcentuales para las cepas A/H1N1, A/H3N2 y B respectivamente, demostrando de nuevo la mayor inmunogenicidad de la vacuna IIV3HD [25].

– Temporada 2012-13 (año 2): La ratio de GMT (IIV3HD/IIV3SD) para la cepa A/H1N1 fue de 1,8 (IC 95% 1,7-1,9) y la diferencia en porcentaje de seroprotección de 5,5 (IC 95% 4,5-6,5). Se obtuvieron resultados similares para las cepas A/H3N2 y B (Tabla 2). Además, como en las temporadas 2011-12 y en la 2012-13 la cepa A/H1N1 vacunal fue la misma, se pudo estimar la GMT ratio combinada para ambas temporadas, que fue de 1,8 (IC 95% 1,7-1,9) y la diferencia en porcentaje de seroprotección en el conjunto de las dos temporadas, que fue de 4,8 (IC 95% 4,1-5,5) [25]. Todos estos datos demuestran una respuesta inmunogénica superior de la vacuna de alta dosis en comparación con la vacuna de dosis estándar a lo largo del tiempo o con la vacunación consecutiva.

Subanálisis de los ensayos clínicos de inmunogenicidad. El impacto de la edad, la fragilidad o la comorbilidad en la inmunogenicidad de la vacuna de alta dosis se evaluó en un subanálisis del estudio de fase IIIb/IV FIM12 [20]. Las GMT de los títulos HIA fueron significativamente mayores entre los participantes inmunizados con la vacuna IIVHD, para todas las cepas y en todos los subgrupos de interés (edad, comorbilidades de riesgo y fragilidad) (Tabla 3). En general, las GMT de los títulos HIA postvacunación tendieron a ser mayores frente al componente A/H3N2 de la vacuna en el primer año (A/Victoria/210/2009) y menores frente al componente B en el segundo año (B/Texas/6/2011). Las ratios de las GMT (IIVHD/IIVSD) oscilaron entre 1,24 y 2,09 (estando los límites inferiores del intervalo de confianza de todas las estimaciones por encima de 1) [20]. Por consiguiente, la superior inmunogenicidad proporcionada por la vacuna IIV3HD es independiente de la edad, la comorbilidad y la fragilidad del vacunado.

Resulta interesante señalar también el efecto inmune en individuos vacunados frente a la gripe en la estación previa. En el subanálisis del estudio aleatorizado FIM12 para evaluar este parámetro, se observó que los títulos HIA postvacunación fueron también significativamente más altos (de 1,5 a 2 veces) en los participantes que recibieron IIV-HD en el segundo año en comparación con aquellos que recibieron IIV-SD, independientemente de la vacuna que recibieron durante el primer año [15].

Metaanálisis de inmunogenicidad: Inmunogenicidad comparativa de la vacuna de alta dosis frente a la vacuna de dosis estándar. Los resultados de varios metaanálisis en los que se ha evaluado la inmunogenicidad de la vacuna IIV3HD se resumen en la Tabla 4. En el metaanálisis de Samson et al. [26], que incluyó siete ensayos clínicos con más de 18.500 sujetos, las ratios de las GMT IIV3HD/IIV3SD combinadas, se estimaron en 1,74 (IC 95% 1,65-1,83) para la cepa A/H1N1, 1,84 (IC 95% 1,73-1,95) para la cepa A/H3N2 y 1,47 (IC 95% 1,36-1,58) para la cepa B. Este metaanálisis confirmó que la vacuna IIV3HD era más inmunogénica en ≥ 65 años independientemente de la edad, la comorbilidad, la fragilidad y los factores de riesgo de los vacunados. Se ha comprobado también una mejor respuesta inmune frente a la neuraminidasa, otro de los antígenos virales implicados en la enfermedad gripal. Múltiples ensayos clínicos aleatorizados incluidos en este metaanálisis [26-28] demostraron que, en general, las ratios de las GMT de los títulos IHA postvacunación y los de anticuerpos antineuraminidasa reportados fueron mayores entre los vacunados con IIV3-HD que en los vacunados con IIV3-SD, tanto en temporadas prepandémicas (2004-2005) [27] como en temporadas postpandémicas [17, 28]. La mayor respuesta inmune en temporadas pre y postpandémicas refuerzan la mayor eficacia observada con la vacuna de alta dosis en estudios aleatorizados frente a gripe confirmada por laboratorio y coincide con la mejor efectividad de la vacuna en la práctica clínica real.

En otro metaanálisis reciente en el que se evaluaron datos de 39 ensayos clínicos aleatorizados que analizaron la inmunogenicidad de vacunas de inmunidad reforzada (VIR), en ≥ 60 años, incluyendo la vacuna IIV3HD, la vacuna adyuvada con MF59 (aIIV3) y la vacuna intradérmica (IDIIV3), se observó que, en general, estas vacunas eran más inmunogénicas que las vacunas de dosis estándar [29]. Entre los participantes inmunizados con VIR se observaron mayores títulos IHA postvacunales frente a todas las cepas incluidas en la vacuna y un mayor porcentaje de individuos con títulos ≥ 40 frente a la mayoría de las cepas. La magnitud de la diferencia en las GMT de títulos HIA postvacunación frente a la cepa A/H3N2 entre las VIR y la vacuna IIV3SD fue más alta para la vacuna de alta dosis (60µg/cepa) (82%, IC 95% 73-91%), seguida de la vacuna adyuvada con MF59 (52%, IC 95% 35-72%) y de la vacuna intradérmica (32%, IC 95% 10-59%). En comparación con la vacuna de dosis estándar, la vacuna IIV3HD indujo una mayor GMT de títulos IHA postvacunación, frente a todas las cepas, que las vacunas aIIV3 y IDIIV3. Entre los sujetos inmunizados con las VIR, una mayor proporción de ellos presentaban títulos IHA postvacunales ≥ 40 que los vacunados con la vacuna de dosis estándar para la mayoría de las cepas A y B. En un análisis conjunto de los datos de todas las vacunas, el porcentaje de los participantes con títulos ≥ 40 entre los inmunizados con la vacuna de alta dosis (60µg/cepa) fue de un 10,4% adicional, en

Tabla 4 **Metaanálisis en los que se ha analizado la inmunogenicidad de la vacuna IIV3-HD**

Autor / año	Tipo de estudio	Temporada	N	Inmunogenicidad (IIV3-HD vs. IIV3-SD)		
Samson et al. 2019 [26]	Revisión sistemática y metaanálisis de inmunogenicidad: - 7 ensayos clínicos aleatorizados	2002 2004-05 2006-07 2007-08 2009-10 2011-12 2012-13	> 18.500	Ratio GMT títulos HIA postvacunación (HD/SD)	A/H1N1	1,7 (1,6 - 1,8)
					A/H3N2	1,8 (1,7 - 2,0)
					B	1,5 (1,4 - 1,6)
Wilkinson et al. 2017 [14]	Metaanálisis con el principal objetivo principal de valorar la eficacia/efectividad y con el objetivo secundario de analizar la inmunogenicidad: - 8 ensayos clínicos	2001-02 2004-05 2006-07 2007-08 2009-10 2011-13	18.215	Diferencia GMT títulos HIA (HD – SD)	A/H1N1	86,2 (47,6 - 124,8)
					A/H3N2	183,2 (84,6 - 285,7)
					B	24,7 (14,1 - 35,3)
Ng et al. 2019 [29]	Revisión sistemática y metaanálisis de inmunogenicidad: - 39 ensayos clínicos	1992-93 a 1994-95	10.492	Ratio GMT títulos HIA postvacunación (HD/SD)	A(H1N1)	1,7 (1,6 - 1,8)
					A(H3N2)	1,8 (1,7 - 1,9)
					B/Yamagata	1,5 (1,3 - 1,7)
					B/Victoria	1,4 (1,3 - 1,6)
		1998-99 2001-02 2002-03		Diferencia GMT títulos HIA (HD – SD)	A(H3N2)	82 (73 - 91)
		2004-05 a 2014-15		Diferencia en % Sujetos con títulos HIA postvacunación ≥ 1:40	A(H1N1)	8,1% (5,2 - 11,0)
					A(H3N2)	3,0% (2,2 – 3,8)
					B/Yamagata	13,5% (11,4 - 15,5)
					B/Victoria	10,4% (7,6 - 13,2)

GMT: títulos medios geométricos; HAI: Inhibición de la hemaglutinación media geométrica; HD: alta dosis, SD: dosis estándar

comparación con los de la vacuna con dosis estándar, siendo del 4,1% tanto para la vacuna adyuvada con MF59 como para la vacuna intradérmica [29]. En este metaanálisis, las GMT con la vacuna de alta dosis mostraron unos valores significativamente mayores que con la vacuna intradérmica y la vacuna adyuvada.

Por último, un metaanálisis cuyo objetivo primario era el análisis de la eficacia/efectividad de la vacuna HD frente a la vacuna SD, incluía también, como objetivo secundario, el análisis comparativo de la inmunogenicidad de ambas vacunas [14]. Incluyó 8 ensayos clínicos realizados en 6 temporadas no consecutivas, pandémica y pre- y postpandémicas y un total de 18.215 sujetos. Los resultados muestran diferencias estadísticamente significativas en las GMT a favor de la vacuna HD, con una mayor diferencia para A/H3N2 (183,2; IC 95% 84,6 - 285,7) (Tabla 4) [14].

SEGURIDAD DE LA VACUNA ANTIGRIPAL TRIVALENTE DE ALTA DOSIS

La vacuna de alta dosis ha demostrado un buen perfil de seguridad, comparable al de la vacuna de dosis estándar; demostrado en ensayos clínicos y en la práctica clínica real [18, 21, 24]. En ninguno de los estudios ni escenarios analizados, se ha observado un incremento desproporcionado en la tasa o la gravedad de las reacciones adversas clínicamente relevantes, respecto a la vacuna de dosis estándar (Tabla 5).

Un estudio de fase III de 2006 en EE. UU., comparando la inmunogenicidad y el perfil de seguridad de la vacuna IIV3HD (n = 2.575) frente a IIV3-SD (n = 1.262) en ≥ 65 años demostró un buen perfil de seguridad de la vacuna IIV3-HD. A pesar de la mayor cantidad de antígeno, las reacciones en el sitio de la inyección fueron generalmente leves o moderadas y se resolvieron en las primeras 72 horas. Las tasas de acontecimientos adversos sistémicos registradas con la vacuna IIV3HD fueron comparables con las de la vacuna IIV3-SD [18]. La reacción observada con más frecuencia para ambas vacunas fue el dolor. Un 36% de los que recibieron IIV3HD reportó dolor de cualquier intensidad, frente al 24% de los que recibieron IIV3SD. La mayoría de los participantes experimentaron dolor de intensidad leve que se resolvió en 72 horas. Otras reacciones locales comunicadas, con incidencia comparable entre ambas vacunas, fueron eritema (15% vs. 11%) e hinchazón (6% vs. 4%),

Tabla 5 **Estudios en los que se evalúa la seguridad de la vacuna IIV3-HD**

Autor / año	Tipo de estudio	Temporada	Cepa dominante	N		Síntoma moderado o grave (IIV3-HD vs. IIV3-SD)		
				IIV3-HD	IIV3-SD			
Ensayos clínicos aleatorizados								
Falsey et al. 2009 [18]	Ensayo clínico fase III	2006-07	A/H1N1	2.576	1.275	Malestar	6,3% vs. 4,2% (RR = 1,5)	
						Mialgia	5,8% vs. 3,4% (RR = 1,7)	
						Dolor de cabeza	4,2% vs. 2,8% (RR = 1,5)	
						Eritema	15% vs.11% (RR = 1,4)	
						Hinchazón	6% vs. 4% (RR = 1,5)	
						Reacciones sistémicas	11% vs. 7% (RR = 1,5)	
						Fiebre	1,1% vs. 0,3% (RR = 3,6)	
						Efectos adversos no esperados	22% vs. 22% (RR = 1,0)	
Tsang et al. 2014 [21]	Ensayo clínico fase II	2007-08	A/H1N1 A/H3N2	320	319	Reacciones solicitadas	61% vs. 46% (RR = 1,3)	
						Reacciones no solicitadas	22% vs. 26% (RR = 0,85)	
						Reacciones no solicitadas relacionadas con el tratamiento	1,6% vs. 1,6% (RR = 1,0)	
						Reacciones en el sitio de inyección	49% vs. 34% (RR = 1,4)	
						Reacciones sistémicas	36% vs. 26% (RR = 1,4)	
DiazGranados et al. 2013 [24]	Ensayo clínico fase IIIb	2009-10	A/H1N1pdm09	6.108	3.050	≥ Evento adversos grave	6,7% vs 6,5%	
						Finalización del estudio debido a eventos graves (ninguno relacionado con la vacunación)	0,5% vs 2,5%	
Subanálisis de EC aleatorizados								
DiazGranados et al. 2016 [15]	Subanálisis del estudio FIM12: seguridad	2011-12 2012-13	A/H3N2	1.942		Cualquier evento adverso grave (180 días siguientes a la vacunación del segundo año)	Año 1 (HD) Año 2 (HD)	6,6%
				1.881			Año 1 (SD) Año 2 (HD)	6,5%
				3.823			Año 1 (HD o SD) Año 2 (HD)	6,5%
				1.891			Año 1 (HD) Año 2 (SD)	7,5%
				1.929			Año 1 (SD) Año 2 (SD)	7,3%
				1.942		Neumonía (en los 180 días siguientes a la vacunación del segundo año)	Año 1 (HD) Año 2 (HD)	0,3%
				1.881			Año 1 (SD) Año 2 (HD)	0,4%
				3.823			Año 1 (HD o SD) Año 2 (HD)	0,4%
				1.891			Año 1 (HD) Año 2 (SD)	0,8%
				1.929			Año 1 (SD) Año 2 (SD)	0,6%
				1.942		Muerte (en los 180 días siguientes a la vacunación del segundo año)	Año 1 (HD) Año 2 (HD)	0,1%
				1.881			Año 1 (SD) Año 2 (HD)	0,4%
				3.823			Año 1 (HD o SD) Año 2 (HD)	0,2%
				1.891			Año 1 (HD) Año 2 (SD)	0,3%

HD: alta dosis, SD: dosis estándar

que generalmente también se resolvieron en 72 horas. Aunque las reacciones locales fueron significativamente más frecuentes con IIV3HD, la diferencia real del tamaño medio de la zona máxima de eritema o hinchazón fue ≤ 5 mm y la diferencia en la media de la puntuación máxima en la escala de dolor, muy modesta (1,12 vs. 1,08) [18].

Las reacciones sistémicas específicamente solicitadas a cada sujeto durante los 7 primeros días tras la vacunación (fiebre de cualquier grado, dolor de cabeza, malestar o mialgia) fueron de frecuencia comparable entre las dos vacunas (IIV3HD 34% vs. IIV3SD 29%). Aunque se observó un mayor riesgo relativo (RR) de fiebre moderada o grave con la vacuna de alta dosis (RR 3,6; IC 95% 1,25-10,08), el número de individuos afectados fue relativamente bajo con ambas vacunas (1,1% vs. 0,3%), siendo generalmente casos moderados. Solo se detectó un caso de fiebre grave en cada uno de los grupos de tratamiento. Asimismo, las tasas de reacciones adversas no solicitadas durante los 28 días posteriores a la vacunación fueron comparables en ambas vacunas; siendo un 23% en el grupo de IIV3HD y un 21% en el de IIV3SD. A lo largo del estudio no se registró ningún fallecimiento relacionado con la vacunación en ninguno de los dos grupos [18].

Un ensayo clínico de fase II, aleatorizado, en EE. UU proporcionó datos adicionales sobre la seguridad y tolerabilidad de la vacuna IIV3HD. Se aleatorizaron sujetos ≥ 65 años (n=320) que recibieron la vacuna IIV3HD y otros que recibieron la vacuna IIV3SD (n = 319) o una vacuna trivalente intradérmica inactivada (IID3) que contenía, o bien 15 µg (IID315) de antígeno HA por cepa (n = 636), o 21 µg (IID321, n = 634). Como comparador, se vacunaron adultos jóvenes (18-49 años), con la vacuna IID3-15. En general, las reacciones solicitadas fueron en su mayoría leves o moderadas y de resolución rápida con todas las vacunas. Sin embargo, fueron más frecuentes con cualquier vacuna intradérmica (79,1% con la vacuna IID3-15 y 79,9% con la IID3-21), que con la vacuna IIV3HD (60,8%) o la IIV3SD (45,8%). Las reacciones no solicitadas también fueron más frecuentes con vacuna intradérmica (2,7% con la vacuna IID315 y 2,4% con la IID321) que con la vacuna IIV3HD o la vacuna IIV3SD (1,6% para ambas). No se registraron reacciones adversas graves con ninguna de las vacunas. Este estudio confirmó los resultados anteriores de otros autores, demostrando la buena tolerabilidad de la vacuna trivalente de alta dosis y la ausencia de reacciones adversas graves [21].

Otro estudio de fase IIIb, en EE. UU, durante la temporada pandémica 200910, también demostró la seguridad y tolerabilidad de la vacuna IIV3HD en ≥ 65 años, en comparación con la vacuna IIV3-SD. Los acontecimientos adversos de especial interés fueron muy poco frecuentes y solo un 0,5% de los participantes en ambos grupos de vacunación abandonaron el estudio debido a acontecimientos adversos graves [24].

Tampoco se han detectado problemas de seguridad con IIV3HD en sujetos inmunizados durante temporadas consecutivas. En un subanálisis del estudio FIM12 (EE. UU y Canadá, dos temporadas de 2011 a 2013) [15] no se detectaron episodios relacionados con la seguridad en la reinmunización con la vacuna IIV3HD en el grupo de sujetos (n = 7.465) que se revacunaron en el segundo año del estudio.

NUEVA VACUNA CUADRIVALENTE DE ALTA DOSIS

Ya está autorizada por la Agencia Española del Medicamento y Productos Sanitarios la formulación cuadrivalente de la vacuna de alta dosis [30]. La seguridad y la inmunogenicidad de la vacuna IIV4-HD en ≥ 65 años se evaluó en el estudio de fase III aleatorizado, QHD00013 [31]. Las GMT de los títulos IHA y las tasas de seroconversión inducidas por la vacuna IIV4-HD no fueron inferiores respecto a las cepas comunes contenidas en la vacuna IIV3-HD [31]. Sin embargo, las GMT de los títulos IHA y las tasas de seroconversión fueron mayores para las dos cepas B, con la vacuna IIV4-HD. Las GMT (IIV4HD/IIV3HD) fueron 2,03 (1,802-2,288) para la cepa B/Victoria y 2,04 (1,804-2,315) para la cepa B/Yamagata; las diferencias en la tasa de seroconversión entre ambas vacunas (IIV4-HD– IIV3-HD) fueron del 20,78% (16,5-24,61) para la cepa B/Victoria y del 29,27% (24,78-33,29) para la cepa B/Yamagata. Además, este estudio confirmó que la inclusión de dos cepas de gripe B no modificaba el perfil de seguridad de la vacuna IIV4-HD, que fue muy similar al de la vacuna IIV3-HD [31].

CONCLUSIONES

Los estudios de inmunogenicidad, llevados a cabo con la vacuna IIV3-HD en más de 17.000 personas ≥65 años, ponen de manifiesto una mayor respuesta inmune, en términos de anticuerpos, respecto a otros tipos de vacunas, como la vacuna de dosis estándar o la vacuna de administración intradérmica.

Los títulos de anticuerpos obtenidos con la vacuna de alta dosis son significativamente mayores para las cepas A/H1N1 y A/H3N2 respecto a los obtenidos con la vacuna adyuvada.

La mayor inmunogenicidad de la vacuna IIV3-HD se asocia a un perfil de seguridad similar al de la vacuna de dosis estándar.

AGRADECIMIENTOS

Los autores agradecen la ayuda de Luis F. García-Fernández, PhD y Vanessa Marfil, PhD (Medical Statistics Consulting, Valencia, España) en la redacción y edición de este manuscrito.

CONFLICTOS DE INTERESES

ROL ha percibido honorarios por ponencias y consultoría científica de Sanofi Pasteur, GlaxoSmithKline, y Seqirus. FMT ha percibido honorarios por ponencias y consultoría científica de GlaxoSmithKline, Pfizer, Sanofi Pasteur, Merck Sharp & Dohme, Seqirus y Janssen. Ha participado como investigador principal en ensayos clínicos patrocinados por GlaxoSmithKline, Pfizer, Sanofi Pasteur, Merck Sharp & Dohme, Seqirus, Janssen, Ablynx, Regeneron, Roche, Abbott, Novavax, y MedImmune, por los que su institución ha percibido honorarios.

Ha recibido financiación para proyectos de investigación del Instituto de Salud Carlos III (Proyecto de Investigación en Salud, Acción Estratégica en Salud PI1901090) del plan nacional de I+D+I y fondos FEDER. AGM ha percibido honorarios por ponencias y consultoría científica, ayudas para viajes y patrocinio de proyectos de investigación de Sanofi Pasteur, Merck Sharp and Dohme, GlaxoSmithKline, Seqirus y Pfizer. JDD ha percibido honorarios por consultoría científica de Sanofi Pasteur y GlaxoSmithKline. FISABIO recibe colaboración para proyectos de investigación de Sanofi Pasteur y GlaxoSmithKline. ERM ha percibido honorarios por ponencias y consultoría científica así como ayudas para viajes o asistencia a cursos de GlaxoSmithKline, Sanofi Pasteur, Merck Sharp & Dohme, Pfizer, Novartis y Faes Farma.

FINANCIACIÓN

Sanofi ha promovido el desarrollo de este trabajo financiando los servicios de *medical writing* y facilitando las reuniones del panel de expertos. Los autores han desarrollado y consensuado el contenido con independencia de la fuente de financiación.

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/082.2020

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Incidencia de nefrotoxicidad inducida por colistina intravenosa en pacientes hospitalizados

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Article history
Received: 26 July 2020; Revision Requested: 21 August 2020; Revision Received: 21 September 2020; Accepted: 19 October 2020; Published: 19 November 2020

RESUMEN

Objetivos. El incremento de infecciones por bacterias multirresistentes ha obligado a retomar el uso de colistina, antibiótico con nefrotoxicidad conocida. El objetivo del estudio es determinar la incidencia de nefrotoxicidad por colistina en la actualidad.

Material y métodos. Estudio retrospectivo, observacional y unicéntrico que recoge los pacientes hospitalizados en tratamiento con colistina intravenosa durante los años 2018-2019. Se excluyeron los pacientes ingresados en unidades de cuidados críticos. Se definió la nefrotoxicidad según la escala RIFLE. Las variables para determinarla fueron creatinina sérica (Crs) y filtrado glomerular (FG). Las variables analizadas fueron: edad, sexo, duración de tratamiento, dosis de carga y acumulada, tratamiento empírico/dirigido, enfermedad renal crónica, uso de contrastes intravenosos y fármacos nefrotóxicos concomitantes.

Resultados. Se incluyeron 90 pacientes (60% hombres), con una media de edad de 58,2±18,1 años. La media de duración de tratamiento fue de 9±8,3 días, con una media de dosis acumulada de 69,8±71MU. No hubo diferencias entre Crs y FG al inicio y final del tratamiento. La incidencia de nefrotoxicidad fue de 1,73 casos/100 días de tratamiento (prevalencia del 15,56%).

Conclusión. La nefrotoxicidad por colistina presenta una incidencia importante, sin desarrollar cuadros graves.

Palabras clave: Colistina, toxicidad farmacológica, factores de riesgo.

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Incidence of intravenous colistin nephrotoxicity in hospitalized patients

ABSTRACT

Objectives. The increase in infections with multidrug resistant bacteria has forced to return to the use of colistin, antibiotic with known nephrotoxicity. The aim of the study is to determine the incidence of colistin nephrotoxicity nowadays.

Material and methods. Retrospective-observational-unicentric study was collected hospitalized patients in intravenous colistin treatment during the years 2018-2019. Nephrotoxicity was defined according to the RIFLE scale. The variables to determine it were serum creatinine (sCr) and glomerular filtration (GF). The variables analyzed were age, sex, treatment duration, loading and cumulative dose, empirical/targeted treatment, chronic kidney disease, concomitant use of intravenous contrast and nephrotoxic drugs.

Results. A total of 90 patients (60% men) were included, with an average age of 58.2±18.1 years. The mean duration of treatment was 9±8.3 days, with an average cumulative dose of 69.8±71MU. There were no differences between sCr and GF at the beginning and end of treatment. The incidence of nephrotoxicity was 1.73 cases/100 days of treatment (prevalence of 15.56%).

Conclusions. Colistin nephrotoxicity has an important incidence, without developing severe illness.

Keywords: colistin, drug toxicity, risk factors.

INTRODUCCIÓN

Colistina es un antibiótico de la familia de las polimixinas. Presenta actividad contra bacilos gramnegativos (BGN), siendo de especial utilidad en el tratamiento de las infecciones por *Pseudomonas aeruginosa* resistente. Una de sus principales limitaciones es la toxicidad renal, posiblemente mediada por

su acumulación intracelular, en las mitocondrias de las células renales [1]. Este hecho, junto con la aparición de otras alternativas antibióticas más seguras en la época, hicieron que colistina dejara de ser una opción terapéutica de primera línea en los años 50 y 60 [2].

El incremento de infecciones por bacterias multirresistentes, unido a un período de escasas innovaciones en los tratamientos antibióticos [3], hizo que se retomase el uso de colistina para el tratamiento de estas infecciones, siendo comercializada en España en su presentación intravenosa (colistimetato sódico) en el año 2004 [4].

Se han incorporado recientemente al arsenal terapéutico nuevos antibióticos activos contra BGN multirresistentes [5], con un perfil de seguridad favorable. No obstante, las políticas de racionalización del uso de antibióticos en el ámbito hospitalario [6] han hecho que su uso sea reservado para las infecciones más graves. En este contexto, el uso de colistina evitaría en parte la presión selectiva, fomentando la diversificación de antibióticos antipseudomónicos.

A pesar de que los datos de nefrotoxicidad datan de sus inicios, la información sobre la farmacocinética y farmacodinamia (PK-PD) de colistina ha sido limitada, impidiendo con ello el utilizar unas pautas estandarizadas de tratamiento [2]. Datos más actualizados sobre el perfil PK-PD han permitido elaborar un consenso sobre las pautas posológicas [7]. Esto hace interesante el poder verificar cuál es la incidencia de nefrotoxicidad en la práctica clínica actual, donde se utilizan pautas posológicas estandarizadas, y de qué forma influyen en ella las diferentes características demográficas y clínicas de los pacientes.

El objetivo del estudio es determinar la incidencia de nefrotoxicidad inducida por colistina intravenosa en los pacientes hospitalizados en nuestro centro.

MATERIAL Y METODOS

Se trata de un estudio retrospectivo, observacional y unicéntrico donde se recogen los pacientes en tratamiento con colistina intravenosa en forma de colistimetato sódico (CMS), durante los años 2018 y 2019. Se incluyeron aquellos pacientes que iniciaron y finalizaron el tratamiento durante su ingreso hospitalario, manteniendo la terapia antibiótica durante al menos 4 días consecutivos.

Los datos se obtuvieron a través de una descarga desde la prescripción integrada en la historia clínica electrónica. El criterio de nefrotoxicidad se definió acorde la escala RIFLE [8], la cual estratifica la nefrotoxicidad según las etapas de la lesión renal en orden de gravedad creciente: riesgo, daño y fallo renal. Las variables recogidas para determinar la nefrotoxicidad inducida por colistina fueron el valor de creatinina sérica (Crs) y filtrado glomerular estimado (FG) tanto al inicio como al final del tratamiento. El valor de FG se calculó mediante la fórmula CKD-EPI. Se realizó el análisis estadístico a través de la herramienta de análisis de datos de Microsoft 365 Excel® (Microsoft Corporation).

Las variables analizadas con posible relación con la nefrotoxicidad fueron: edad, sexo, duración de tratamiento, dosis de carga y mantenimiento de CMS (en millones de unidades, MU), tratamiento empírico/dirigido, diagnóstico previo de enfermedad renal crónica (ERC) (definida como la presencia de filtrado glomerular menor a 60 ml/min por un período de 3 meses o superior), uso de contrastes intravenosos (CIV) durante el tratamiento y prescripción concomitante de fármacos nefrotóxicos [9] (antibióticos, antivirales, antifúngicos, inmunosupresores, antiinflamatorios no esteroideos, etc.).

Otras variables recogidas fueron: unidad de hospitalización, diagnóstico infeccioso, motivo de fin de tratamiento, requerimiento de terapias de reemplazo renal durante el tratamiento.

La pauta posológica de colistina se utilizó según indicaciones de ficha técnica [4]. En el caso de diagnóstico de neutropenia febril en pacientes onco-hematológicos, se siguió la siguiente pauta según protocolo interno del centro: dosis de carga de 9MU el día 1, seguido de 4,5MU cada 12 horas los días posteriores hasta resultados de hemocultivos y antibiograma. Ante aclaramiento de creatinina inferior a 50 ml/min, se reducirán las dosis de carga y mantenimiento a 6MU y 3MU, respectivamente. Si no se disponen de información microbiológica, se mantendrá tratamiento si se observa mejoría clínica. Se debe reevaluar la continuidad de tratamiento a los 7 días desde el inicio.

El estudio de asociación entre las variables cuantitativas se realizó mediante la prueba t de Student, mientras que en las variables cualitativas se utilizó la prueba de Chi cuadrado. Se consideró un nivel de significación estadística de $p<0,05$.

RESULTADOS

Se incluyeron un total de 90 pacientes. Las características generales de los pacientes, así como las características de aquellos que desarrollaron nefrotoxicidad y los que no, se encuentran en la Tabla 1. De la misma manera, en la Tabla 2 se encuentran las características referidas al tratamiento con colistina y al uso de fármacos nefrotóxicos y contrastes intravenosos concomitantes.

La mediana de fármacos nefrotóxicos concomitantes fue de 1 fármaco/paciente [RI 0-1], siendo aciclovir (48,28%), vancomicina (18,39%) y amikacina (10,34%) los más frecuentes. No hubo diferencias entre la creatinina y FG al inicio y final del tratamiento.

La incidencia global de nefrotoxicidad (considerando las tres etapas de la escala RIFLE) fue de 1,73 casos por cada 100 días de tratamiento, lo que supone una prevalencia del 15,56% en los dos años de estudio. Estratificando por las etapas de la lesión renal, la incidencia de riesgo renal fue de 0,99 casos por cada 100 días de tratamiento, mientras que la de daño renal fue de 0,74 casos por cada 100 días de tratamiento. No hubo ningún caso de fallo renal.

Tabla 1 **Características de los pacientes y diferencias encontradas entre los pacientes que desarrollaron nefrotoxicidad y quienes no lo hicieron.**

	Todos los pacientes (%) (n=90)	Pacientes con nefrotoxicidad (%) (n=14)	Pacientes sin nefrotoxicidad (%) (n=76)	P
Edad media (años) ± DE	58,2±18,1	59,3±16,5	58±18,2	0,81
Sexo				
Mujeres	36 (40)	8 (57,1)	28 (36,8)	0,15
Hombres	54 (60)	6 (42,9)	48 (63,2)	
Diagnóstico de ERC previo				
Sí	15 (16,7)	1 (7,1)	14 (18,4)	0,71
No	75 (83,3)	13 (92,9)	62 (81,6)	
Tratamiento con terapia de reemplazo renal				
Sí	4 (4,4)	1 (7,1)	3 (3,9)	0,47
No	86 (95,6)	13 (92,9)	73 (96,1)	
Motivo de uso de colistina				
Neutropenia febril	46 (51,1)	7 (50)	39 (51,3)	
Infección respiratoria	14 (15,6)	3 (21,4)	11 (14,5)	
Infección quirúrgica	9 (10)	0 (0)	9 (11,8)	
Sepsis	8 (8,9)	3 (21,4)	5 (6,6)	
Otras infecciones	13 (14,3)	1 (7,1)	12 (15,7)	
Motivos de retirada de tratamiento con colistina				
Fin de tratamiento	72 (80)	9 (64,3)	63 (82,9)	
Toxicidad renal	5 (5,6)	3 (21,4)	2 (2,6)	
Escalado/desescalado del espectro antimicrobiano	6 (6,7)	0 (0)	6 (7,9)	
Limitación del esfuerzo terapéutico	6 (6,7)	1 (7,1)	5 (6,6)	
Éxitus	1 (1,1)	1 (7,1)	0 (0)	
Unidad de hospitalización				
Hematología	52 (57,8)	8 (57,2)	44 (57,9)	
Traumatología	11 (12,2)	2 (14,3)	9 (11,8)	
Neumología	6 (6,7)	0 (0)	6 (7,9)	
Cirugía de digestivo	5 (5,6)	1 (7,1)	4 (5,3)	
Medicina interna	5 (5,6)	0 (0)	5 (6,6)	
Otras	11 (12,1)	3 (21,4)	8 (10,5)	

DE = desviación estándar; ERC = enfermedad renal crónica; P = valor de p.

DISCUSIÓN

La incidencia de nefrotoxicidad observada en nuestro estudio se presentó en su mayoría como una situación de riesgo renal y no como una lesión establecida a este nivel (solo en un 5,56% el motivo de fin de tratamiento fue por deterioro de la función renal). Tras la revisión de la literatura disponible, no se encontraron estudios que determinen la incidencia de nefrotoxicidad por colistina, por lo que nuestro estudio aportaría nueva información al respecto. Sí se encontraron datos de prevalencia, con los que se ha desarrollado la discusión.

La revisión realizada por Ordooei et al. [10] recoge 14 estudios donde se evaluó esta prevalencia de nefrotoxicidad, siendo muy variable en función del estudio revisado (10,9-45%). Nuestros hallazgos se encontrarían dentro de este rango (15,56%). Se utilizó un criterio de evaluación de nefrotoxicidad diferente a la escala RIFLE y se calculó el FG mediante la fórmula de Cockroft-Gault, lo cual puede haber aportado variabilidad en los resultados.

Tabla 2 **Características del tratamiento con colistina y diferencias encontradas entre los pacientes que desarrollaron nefrotoxicidad y quienes no lo hicieron.**

	Todos los pacientes (% (n=90)	Pacientes con nefrotoxicidad (%) (n=14)	Pacientes sin nefrotoxicidad (%) (n=76)	P
Tipo de tratamiento				
Empírico	59 (65,6)	8 (57,1)	51 (67,1)	0,47
Dirigido	31 (34,4)	6 (42,9)	25 (32,9)	
Dosis de carga				
No	25 (27,8)	2 (14,3)	23 (30,3)	<0,01
Sí	65 (72,2)	12 (85,7)	53 (69,7)	
Por dosis de carga utilizada				
Dosis de 9 MU	51	7	44	
Dosis de 6 MU	14	5	9	
Dosis media diaria (MU) ± DE	7,9±1,8	7,7±1,5	7,9±1,9	0,71
Duración media de tratamiento (días) ± DE	9±8,3	9,9±5,8	8,8±8,6	0,67
Acorde al momento de reevaluación del tratamiento				
Duración < 7 días	56 (62,2)	5 (35,7)	51 (67,1)	0,03
Duración ≥ 7 días	34 (37,8)	9 (64,3)	25 (32,9)	
Dosis media acumulada (MU) ± DE	69,8±71	78±53,2	68,3±73,2	0,64
Uso concomitante de contrastes radiológicos intravenosos				
Sí	22 (24,4)	5 (35,7)	17 (22,4)	0,29
No	68 (75,6)	9 (64,3)	59 (77,6)	
Fármacos nefrotóxicos concomitantes				
No	33 (36,7)	5 (35,7)	28 (36,8)	0,94
Sí	57 (63,3)	9 (64,3)	48 (63,2)	
Por número de fármacos				
Con 0 fármacos	33 (36,7)	5 (35,7)	28 (36,8)	
Con 1 fármaco	36 (40)	5 (35,7)	31 (40,8)	
Con 2 fármacos	14 (15,5)	1 (7,1)	13 (17,1)	
Con 3 fármacos	7 (7,8)	3 (21,5)	4 (5,3)	

Vardakas et al. [11] analizaron 5 estudios donde se comparaba colistina frente a polimixina B en el tratamiento de BGN multirresistentes, evaluando también el perfil de seguridad renal. El rango de prevalencia de nefrotoxicidad fue de un 24-74%, superior a la hallada en nuestro estudio. No obstante, los estudios no se plantearon para determinar específicamente nefrotoxicidad. A pesar de que la definición de nefrotoxicidad variaba según el estudio revisado, se realizó la conversión a la escala RIFLE siempre que fue posible.

La revisión de Molina et al. [12] sobre las características farmacocinéticas y farmacodinámicas de las polimixinas, recoge nuevamente una prevalencia de nefrotoxicidad variable (10-27%), encontrándose de nuevo nuestro hallazgo en este rango. La definición de nefrotoxicidad dependió de cada estudio individual.

Martínez et al. [13] analizaron la prevalencia de nefrotoxicidad en pacientes críticos, evaluada mediante la escala RIFLE, siendo esta del 47%. Los pacientes críticos, dada la gravedad de su situación clínica, son más susceptibles de presentar fallos en diferentes órganos, como puede ser el riñón. Esto podría justificar que la prevalencia sea 3 veces superior a la de nuestro estudio, donde la totalidad de los pacientes se encontraban en plantas de hospitalización convencional, entre médicas y quirúrgicas.

Las tres revisiones consultadas [10-12] evaluaron también las posibles variables que influyen en la nefrotoxicidad. A pesar de la gran variabilidad entre los distintos estudios, las variables con mayor influencia fueron: edad, sexo, dosis, duración de tratamiento, fármacos nefrotóxicos concomitantes, hipoalbuminemia, hiperbilirrubinemia, enfermedad subyacente

y gravedad del cuadro clínico. En nuestro estudio, evaluamos las cinco primeras. Además, se incluyeron dos variables que se consideraron en posible relación con el desarrollo de nefrotoxicidad: diagnóstico de ERC y uso de CIV durante el tratamiento con colistina. No se observaron diferencias en la duración del tratamiento como variable continua. Sin embargo, se observó una incidencia mayor de nefrotoxicidad en las pautas iguales o superiores a 7 días de tratamiento (p=0,03). Se realizó el corte en los 7 días al tratarse del momento de reevaluación del tratamiento según el protocolo del centro, además de ser el momento a partir del cual se desarrolla nefrotoxicidad según la bibliografía consultada [10]. Respecto a la dosis, el hecho de recibir o no una dosis de carga fue la única variable que parece aumentar de forma significativa el riesgo de desarrollo de nefrotoxicidad (p<0,01), siendo mayor en aquellos que sí la reciben. El empleo de la dosis de carga es habitual en las infecciones graves, por lo que es una variable de difícil intervención. Tampoco encontramos diferencias significativas entre el uso de CIV y la nefrotoxicidad. La situación de ERC previa, contrario a lo que se esperaba, no influyó en el desarrollo de toxicidad renal, habiendo recibido todos estos pacientes la dosis ajustada a su función renal durante el tratamiento.

Otro aspecto destacable es el alto número de pacientes con tratamiento empírico con colistina. La mayoría presentaban diagnóstico de neutropenia febril, con enfermedad oncohematológica de base. El estudio de Aguado et al. [14] recomienda el uso de colistina en este escenario, en caso de que haya sospecha de bacterias multirresistentes o con producción de carbapenemasas. En este caso, siguiendo el protocolo del centro (adecuado al perfil de resistencias bacterianas del hospital), se utilizaron pautas de tratamiento inferiores a una semana. Acorde a los hallazgos de nuestro estudio, parece justificado este uso con un perfil de seguridad favorable en las pautas cortas de tratamiento.

Las principales limitaciones del estudio han sido el no poder acceder a las prescripciones de aquellas unidades de hospitalización sin prescripción electrónica (unidades de cuidados intensivos) y el hecho de no poder cuantificar la diuresis. El sistema RIFLE [8] es una escala ampliamente utilizada que permite determinar y hacer una clasificación funcional de la insuficiencia renal aguda, pudiendo estratificar su gravedad en función de tres parámetros: Crs, FG y diuresis. Dado que la recogida del valor de diuresis no fue posible en todos los pacientes, se aplicó la escala según los otros dos parámetros.

La nefrotoxicidad por colistina intravenosa presenta una incidencia importante en nuestros pacientes, sin llegar a desarrollar situaciones de afectación renal graves. La duración de tratamiento es la variable donde se ha observado mayor influencia en esta toxicidad, siendo la forma más segura de utilización del antibiótico las pautas inferiores a una semana de tratamiento. La gran variabilidad descrita en la literatura hace necesario estandarizar la selección de pacientes y la metodología de los estudios para arrojar resultados concluyentes en este aspecto.

FINANCIACIÓN

Los autores declaran que no han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/084.2020

Beliefs and attitudes about deprescription in older HIV-infected patients: ICARD Project

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Article history
Received: 29 July 2020; Revision Requested: 18 September 2020; Revision Received: 21 September 2020; Accepted: 6 October 2020; Published: 16 November 2020

ABSTRACT

Objectives. HIV population is aging at an earlier age than those uninfected, requiring more non-HIV medications to treat noncommunicable diseases. In the context of chronic HIV infection, the next therapeutic change would be the polymedication control. This paper has the purpose of explore the attitudes of older people living with HIV toward deprescribing.

Material and methods. This was an observational, prospective and multicenter study conducted from March-April, 2018. People living with HIV (PLWH) on highly active antiretroviral therapy and older than 65 years were included. In addition to demographic and pharmacotherapeutic data, attitudes regarding deprescribing were collected through the "Revised Patients' Attitudes Towards Deprescribing Questionnaire".

Results. A total of 42 patients were included in this study. Regarding their attitudes in relation to deprescription, there were three statements with the most consensuses. The first ("I have a good understanding of the reasons I was prescribed each of my medicines") had 91.9% consensus. The second and third questions showed 89.2% consensus in both cases; "Overall, I am satisfied with my current medicines" and "I like to be involved in making decisions about my medicines with my doctors".

Conclusions. This study is the first to explore the beliefs and attitudes of older PLWH in relation to deprescription process. There are positive attitudes regarding medication knowledge but there also is a percentage of patients who had a negative opinion regarding deprescription. We must study and go deeper in our knowledge of techniques that could help us to better understand their preferences, in order to establish effective and successful deprescription strategies.

KEYWORDS: older HIV; beliefs; attitudes; deprescription

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Identificación de creencias y actitudes relacionadas con la desprescripción en pacientes VIH+ de edad avanzada: Proyecto ICARD

RESUMEN

Objetivos. La población VIH envejece a edades más tempranas que la población no infectada, requiriendo más medicamentos para tratar el resto de enfermedades concomitantes. Por tanto, en el contexto de infección crónica por VIH, el siguiente desafío terapéutico sería el control de la polimedicación. Este trabajo tiene el propósito de explorar las actitudes y creencias de pacientes VIH de edad avanzada con respecto a la desprescripción.

Material y métodos. Se trata de un estudio observacional, prospectivo y multicéntrico realizado desde marzo hasta abril de 2018. Se incluyeron pacientes VIH en tratamiento con terapia antirretroviral mayores de 65 años. Además de datos demográficos y farmacoterapéuticos, se recogieron las actitudes y creencias en relación con la desprescripción a través del cuestionario "Revised Patients' Attitudes Towards Deprescribing".

Resultados. Se incluyeron un total de 42 pacientes. En relación a sus creencias y actitudes, se obtuvo mayor consenso en tres preguntas. La primera ("Entiendo las razones de por qué me han prescrito mis medicamentos") tuvo un consenso del 91,9%. En la segunda ("En general, estoy satisfecho con mis medicamentos actuales") y tercera pregunta ("Me gusta estar involucrado en la toma de decisiones sobre mis medicamentos") se obtuvo un 89,2% de consenso en ambos casos.

Conclusiones. Este estudio es el primero en explorar las creencias y actitudes de pacientes VIH de edad avanzada en relación con la desprescripción. Se han encontrado actitudes po-

sitivas con respecto al conocimiento de la medicación; también existe un porcentaje de pacientes con opinión negativa acerca de la desprescripción. Es necesario profundizar en el conocimiento de técnicas que nos puedan ayudar a entender mejor las preferencias de los pacientes, con el objetivo de establecer estrategias de desprescripción adecuadas y efectivas.

PALABRAS CLAVE: VIH edad avanzada; creencias; actitudes; desprescripción.

INTRODUCTION

The world's HIV population is successfully aging [1] at an earlier age than those uninfected, requiring more non-HIV medications to treat noncommunicable diseases (NCD) [2–4]. The Dutch cohort ATHENA [2] estimates that by 2030, 73% of HIV-infected patients will be over the age of 50, 84% will have at least one comorbidity, and 20% will receive ≥3 non-HIV medications.

Polypharmacy (used of 6 or more drugs) is an increasingly serious public health issue [5]. However, in recent years, the term of "excessive polypharmacy", which describes the use of 10 or more drugs [6], has been introduced. In people living with HIV (PLWH), this is especially worrisome since in some studies the prevalence of polypharmacy and excessive polypharmacy was 56% and 10%, respectively [7]. In the context of chronic HIV infection, the next therapeutic change in these patients would be the polymedication control [8].

The effect of aging and polypharmacy could increase the risk of drug interactions risk and adverse events [8,9], the lack of adherence to HIV and non-HIV medication [8,10], the risk of hospitalizations [8,11], falls [8,12] and death [8,13]. Many of these adverse events could be potentially preventable. All of this leads to the need for greater attention to the aging HIV population, as they are more complex patients than the general population. In addition, it is necessary to establish comprehensive care processes for these patients from all areas, including the pharmacotherapeutic field, always keeping the patient as a priority. At the present time, there is limited knowledge of deprescription in older-PLWH (OPLWH). For this reason, it is necessary to carry out research on this type of intervention in the HIV-infected population.

The aim of this study was to explore the attitudes of OPLWH toward deprescribing. Additionally, we sought to understand whether clinical and demographic characteristics were associated with these attitudes.

MATERIAL AND METHODS

Consent to participate: This study was approved by the Seville-Sur Ethics Committee. All participants provided written informed consent.

Patients. This was an observational, prospective and multicenter study (two centres participated) conducted from March-April, 2018. PLWH on highly active antiretroviral therapy (ART) and older than 65 years were included. All participants provided written informed consent. Patients were followed up by the Pharmaceutical Care Consultation of Viral Diseases from the Hospital Pharmacy Service. Patients participating in clinical trials, with a malign neoplastic or other systemic autoimmune disease as well as those who did not give their written consent were excluded.

The socio-demographic information and comorbidities were collected from the electronic medical record. HIV-related characteristics included route of acquisition, current CD4-T cell count, CD4/CD8 ratio, and ART regimen, among other were also evaluated.

Multimorbidity was defined as the presence of >3 NCD. NCD data records included in this study were: cardiovascular disease, hepatic diseases, metabolic and endocrine disorders (diabetes mellitus), central nervous system diseases, renal diseases (chronic renal failure), lung disease (chronic obstructive pulmonary diseases), neuropsychiatric diseases (depression, dementia, schizophrenia, bipolar disorder, psychosis), and bone disease (osteoporosis, bone fracture).

Regarding pharmacotherapeutic endpoints, we evaluated: type of concomitant medication prescribed, concomitant medication associated with fall risk (loop diuretics, antipsychotics, antidepressants, benzodiazepines, opioids, antiepileptics); ART regimen, polypharmacy, total medication adherence, and complexity index by Medication Regimen Complexity Index (MRCI) [14]. Patients were classified in low MRCI (<11) or high MRCI (≥11) [7], according to the total MRCI (MRCI ART plus concomitant medication). This score has previously been validated [15,16] and applicable to children and adults with HIV. Adherence to ART was measured with the Simplified Medication Adherence Questionnaire (SMAQ) [17] and hospital dispensing records [18]. Adherence to concomitant medication was measure with the Morisky-Green questionnaire (MMAS) [19] and electronic pharmacy dispensing records. For both types of treatment, the multi-interval adherence index will be used for the last 6 months of treatment.

We obtained the number of comorbidities and comedications for other chronic diseases (non-HIV drugs) from review of the medical history and electronic health prescriptions program of Andalusia and La Rioja Public Health System.

Based on the complexity index, the MRCI was calculated using a web tool of Colorado University [14] an adaptation of the score created by Martin *et al.* [15]. This validated tool includes 65 items grouped into three subgroups: dose forms, dosing frequencies, and additional instructions relevant to drug administration.

The Revised Patients' Attitudes Towards Deprescribing (rPATD) Questionnaire (Versions for Older Adults and Caregivers) [20] contains 22 (older adults) and 19 (caregiver) questions, designed to assess individuals' attitudes, beliefs, and experiences regarding their medications, and the potential withdrawal of 1 or more of their medications. The questionnaire has established face, content, criterion, construct, and internal validity, as well as test-retest reliability in Australian older adults [20]. The results are self-reported attitudes, are not medication spe-

cific, and are hypothetical in relation to intentions. These statements had response categories of "strongly agree," "agree,", "I am not sure", "disagree," and "strongly disagree". We used the Spanish version of rPATD, adapted by De Juan *et al*. [21].

Statistical analysis. Discrete variables were expressed as counts (percentage) and continuous variables as medians and interquartile ranges (IQRs) or means and standard deviation (SD). Differences in categorical variables were calculated using a two-sided likelihood ratio chi-square test or Fisher exact test, and the t-student test or Mann-Whitney nonparametric test were used for continuous variables, when appropriate. The adjustment or not to normality will be verified by means of the Kolmogorov-Smirnov or Shapiro-Wilk tests, according to the size of the groups.

Participant responses to the questions in the Medication Attitudes module are reported as proportions. We focused on three of the rating-scale statements as the main outcomes of interest as they had more consensuses in their answers. A 5-category scale from strongly disagree to strongly agree was employed. The responses to these questions were converted to a binary variable of agree (strongly agree or agree) and disagree (I am not sure, disagree or strongly disagree), which was then examined using logistic regression to assess unadjusted associations between the three main statements and respondents' demographic and clinical characteristics. A logistic regression model was then used to assess the the likelihood of willingness to stop and wanting to reduce drugs use after adjusting for demographic and clinical characteristics. Data were analyzed using IBM SPSS Statistics version 20.0 software. The threshold for statistical significance was defined as $p<0.05$.

Ethics statement. This study was approved by the Seville-Sur Ethics Committee (reference 0628-N-18). All participants provided written informed consent.

RESULTS

A total of 42 patients were included in this study and 78.6% (n =33) were male. The median age was 70 years [IQR = 68-76]. Thirty-seven patients answered the survey themselves; in five cases, the caregiver provided the answer. The baseline features characteristics of the patients are shown in Table 1. Table 2 also showed the attitudes of the patients about the three most consensuses.

Regarding their beliefs and attitudes in relation to deprescription reported by the own patients, the results were heterogeneous. The answer to each question asked to both patients and caregivers are shown in Figure 1 and 2, respectively. Three were the statements with the most consensuses. The first ("I have a good understanding of the reasons I was prescribed each of my medicines") had 91.9% consensus (agree or strongly agree). The second and third questions showed 89.2% consensus (agree or strongly agree) in both cases; "Overall, I am satisfied with my current medicines" and "I like to be involved in making decisions about my medicines with my doctors".

Other statement with broad consensus and special relevance to the issue of attitudes towards deprescription was "If my doctor said it was possible, I would be willing to stop one or more of my regular medicines"; 83.8% consensus (agree or strongly agree). The last interesting statement having a high consensus showed 73% consensus (strongly disagree or disagree); "I think one or more of my medicines may not be working".

In the caregiver´s questionnaire, we can highlight four statements, all of them 100% consensus (agree or strongly agree): "Overall, I am satisfied with my care recipient's current medicines"; "I always ask the doctor, pharmacist or other healthcare professional if there is something I don't understand about my care recipient's medicines"; "I know exactly what medicines the person that I care for is currently taking and/or I have an up-to-date list of their medicines"; and "If their doctor said it was possible I would be willing to stop one or more of my care recipient's medicines". On the other hand, 80% of caregivers (agree or strongly agree) felt that "My care recipient's medicines are a burden to them".

The results of the univariate analysis were heterogeneous, so we did not perform a multivariate analysis subsequently. Relevant results were shown in Table 2. We could argument, on the basis of the univariate analysis that, on the question "I have a good understanding of the reasons I was prescribed each of my medicines", people with cardiovascular disease seemed to be more in agreement with this issue ($p= 0.048$; [95% Confidence Interval (CI) 0.968-1.673]. The same happened with patients with triple-therapy in comparison with mono or bi-therapy [both considered as Less-Drug Regime (LDR)], $p= 0.015$; [95% CI 0.952-2.143]. Regarding question "Overall, I am satisfied with my current medicines", having no central nervous system pathology was positively related to being satisfied with treatment, $p= 0.026$; [95% CI 0.005-0.693]. In contrast, patients with central nervous system pathology were 16.8 times more likely to be dissatisfied with their treatment. Patients who were not polymedicated were 1.33 times more likely to say that they are satisfied with their medication, $p= 0.028$; [95% CI 1.005-1.769].

DISCUSSION

We explored the attitudes of OPLWH toward deprescribing. These patients showed positive attitudes regarding their medication knowledge and concerned to be properly informed about medications they were taking. Something similar are reported by caregivers. However, regarding to the discomfort of taking medication, there was no clear consensus, showing that not all patients were uncomfortable taking their medication. By contrast, there was a higher percentage of caregivers who thought that the medicines taken by the person they care for, were a burden on them. Also, they felt that the person they care for was taking too many medicines. It is important to keep in mind that the opinions about therapy of the patients differ from the opinions of the people who take care of them. Without a doubt this will force us to establish a therapeutic consensus with our patients.

Table 1 Caracteristics of older adults

Respondent Characteristics	Total (n=42)
Age (years); n (%)	
< 70	20 (47.6)
≥ 70	22 (52.4)
Sex; n (%)	
Men	33 (78.6)
Women	9 (21.4)
Nationality; n (%)	
Spanish	39 (92.9)
Others	3 (7.1)
Education; n (%)	
Being able to read but no studies/primary studies	37 (88.1)
High school/completed university studies	5 (11.9)
Patient/caregiver relationship (if caregiver survey); n (%)	
Son/daughter	4 (80)
Other relationship	1 (20)
Patient's Residence; n (%)	
Unaccompanied home	12 (28.6)
Home with relatives/ Nursing homes	30 (71.4)
Acquisition risk factor; n (%)	
Sexual	37 (88.1)
Parenteral	5 (11.9)
Viral load; n (%)	
Undetectable (< 50 copies/mL)	41 (97.6)
Detectable (> 50 copies/mL)	1 (2.4)
CD4 (cell/µL); n (%)	
< 200 cell/µL	5 (11.9)
≥ 200 cell/µL	37 (88.1)
CD4/CD8; n (%)	
< 0.7	22 (52.4)
≥ 0.7	20 (47.6)
Viral Hepatopathies; n (%)	
Yes	7 (16.7)
No	35 (83.3)
Dyslipemia; n (%)	
Yes	31 (73.8)
No	11 (26.2)
Central nervous system diseases; n (%)	
Yes	8 (19.1)
No	34 (80.9)
Cardiovascular risk; n (%)	
Yes	18 (42.9)
No	24 (57.1)
Hypertension; n (%)	
Yes	19 (45.2)
No	23 (54.8)
Diabetes mellitus; n (%)	
Yes	28 (66.7)
No	14 (33.3)
Other comorbidities (total number); n (%)	
< 1	10 (23.8)
≥ 1	32 (76.2)
Total number of comorbidities; n (%)	
< 3	11 (26.2)
≥ 3	31 (73.8)
Pluripathological patient (3 or more diseases)	
N, (%)	32 (76.2)
Type of concomitant medication prescribed; n (%)	
Antiulcerous /antiacids	19 (45.2)
Psychoactive drugs	10 (23.8)
Hypolipemics	28 (66.7)
Antihypertensive and cardiovascular risk drugs	29 (69.0)
Antidiabetics	12 (28.6)
Concomitant medication associated with fall risk; n (%)	
Yes	19 (45.2)
No	23 (54.8)
Type of ART therapy; n (%)	
Two NRTI plus NNRTI	8 (19.1)
Two NRTI plus b/PI	5 (11.9)
Two NRTI plus INSTI	18 (42.8)
Others	11 (26.2)
ART situation; n (%)	
Naive	4 (9.5)
Rescue	9 (21.4)
Multifailure	29 (69.1)
Therapy type; n (%)	
Monotherapy	2 (4.7)
Bitherapy	8 (19.1)
Triple-therapy	32 (76.2)
Polymedicated patients (≥6 drugs, including ART)	
N, (%)	20 (47.6)
Total medication adherence	
N, (%)	31 (73.8)
Complexity index by MRCI; n (%)	
Low MRCI (< 11)	18 (42.9)
High MRCI (≥ 11)	24 (57.1)

NRTI; nucleoside reverse transcriptase inhibitors, NNRTI; non-nucleoside reverse transcriptase inhibitor, b/PI; boosted protease inhibitor, INSTI; integrase strand transfer inhibitor, MRCI; Medication Regimen Complexity Index

Table 2 Statistical results of the univariate analysis

Respondent characteristics	"I have a good understanding of the reasons I was prescribed each of my medicines" (n=37)		p	OR (95% CI)	"Overall, I am satisfied with my current medicines" (n=37)		p	OR (95% CI)	"I like to be involved in making decisions about my medicines with my doctors" (n=37)		p	OR (95% CI)
	Disagree n (%)	Agree n (%)			Disagree n (%)	Agree n (%)			Disagree n (%)	Agree n (%)		
Age (years); n (%)												
< 70	1 (2.7)	18 (48.7)	0.604	-	2 (5.4)	17 (46)	1.000	-	2 (5.4)	17 (46)	1.000	-
≥ 70	2 (5.4)	16 (43.2)		-	2 (5.4)	16 (43.2)		-	2 (5.4)	16 (43.2)		-
Sex; n (%)												
Men	2 (5.4)	28 (75.7)	0.477	-	3 (8.1)	27 (73)	1.000	-	4 (10.8)	26 (70.3)	0.570	-
Women	1 (2.7)	6 (16.2)		-	1 (2.7)	6 (16.2)		-	0 (0.0)	7 (18.9)		-
Education; n (%)												
Being able to read but no studies/primary studies	3 (8.1)	29 (78.4)	1.000	-	4 (10.8)	28 (75.7)	1.000	-	4 (10.8)	28 (75.7)	1.000	-
High school/completed university studies	0 (0.0)	5 (13.5)		-	0 (0.0)	5 (13.5)		-	0 (0.0)	5 (13.5)		-
Patient's Residence; n (%)												
Unaccompanied home	0 (0.0)	11 (29.7)	0.457	-	0 (0.0)	11 (29.7)	0.341	-	1 (2.7)	10 (27.0)	0.909	-
Home with relatives/ Nursing homes	3 (8.1)	23 (62.2)		-	4 (10.8)	22 (59.5)		-	3 (8.1)	23 (62.2)		-
Viral load; n (%)												
Undetectable (< 50 copies/mL)	3 (8.1)	33 (89.2)	1.000	-	4 (10.8)	32 (86.5)	1.000	-	4 (10.8)	32 (86.5)	1.000	-
Detectable (> 50 copies/mL)	0 (0.0)	1 (2.7)		-	0 (0.0)	1 (2.7)		-	0 (0.0)	1 (2.7)		-
CD4 (cell/µL); n (%)												
< 200 cell/µL	1 (2.7)	3 (8.1)	0.298	-	0 (0.0)	4 (10.8)	1.000	-	0 (0.0)	4 (10.8)	1.000	-
≥ 200 cell/µL	2 (5.4)	31 (83.8)		-	4 (10.8)	29 (78.4)		-	4 (10.8)	29 (78.4)		-
Viral Hepatopathies; n (%)												
No	3 (8.1)	27 (73.0)	1.000	-	4 (10.8)	26 (70.3)	0.570	-	4 (10.8)	26 (70.3)	0.570	-
Yes	0 (0.0)	7 (18.9)		-	0 (0.0)	7 (18.9)		-	0 (0.0)	7 (18.9)		-
Dyslipemia; n (%)												
No	1 (2.7)	10 (27.0)	1.000	-	1 (2.7)	10 (27.0)	1.000	-	3 (8.1)	23 (62.2)	1.000	-
Yes	2 (5.4)	24 (64.9)		-	3 (8.1)	23 (62.2)		-	1 (2.7)	10 (27.0)		-
Central nervous system diseases; n (%)												
No	2 (5.4)	27 (73.0)	0.530	-	1 (2.7)	28 (75.7)	0.026 (Yes)	16.800 (1.442-195.676)	3 (8.1)	26 (70.3)	1.000	-
Yes	1 (2.7)	7 (18.9)		-	3 (8.1)	5 (13.5)			1 (2.7)	7 (18.9)		-

Table 2 Statistical results of the univariate analysis (cont.)

Respondent characteristics	"I have a good understanding of the reasons I was prescribed each of my medicines" (n=37)		p	OR (95% CI)	"Overall, I am satisfied with my current medicines" (n=37)		p	OR (95% CI)	"I like to be involved in making decisions about my medicines with my doctors" (n=37)		p	OR (95% CI)
	Disagree n (%)	Agree n (%)			Disagree n (%)	Agree n (%)			Disagree n (%)	Agree n (%)		
Cardiovascular risk; n (%)												
No	0 (0.0)	23 (62.2)	0.047	1.273 (0.968-1.673)	2 (5.4)	21 (56.8)	0.625	-	2 (5.4)	21 (56.8)	0.625	-
Yes	3 (8.1)	11 (29.7)			2 (5.4)	12 (32.4)		-	2 (5.4)	12 (32.4)		-
Hypertension; n (%)												
No	1 (2.7)	17 (46.0)	1.000	-	1 (2.7)	17 (46.0)	0.604	-	1 (2.7)	17 (46.0)	0.604	-
Yes	2 (5.4)	17 (46.0)		-	3 (8.1)	16 (43.2)		-	3 (8.1)	16 (43.2)		-
Diabetes mellitus; n (%)												
No	3 (8.1)	21 (56.8)	0.538	-	3 (8.1)	21 (56.8)	1.000	-	3 (8.1)	21 (56.8)	0.276	-
Yes	0 (0.0)	13 (35.1)		-	1 (2.7)	12 (32.4)		-	0 (0.0)	13 (35.1)		-
Type of concomitant medication prescribed; n (%)												
Antiulcerous / antiacids	2 (5.4)	14 (37.8)	0.568	-	3 (8.1)	13 (35.1)	0.296	-	3 (8.1)	13 (35.1)	0.296	-
Psychoactive drugs	1 (2.7)	7 (18.9)	0.530	-	1 (2.7)	7 (18.9)	1.000	-	1 (2.7)	7 (18.9)	1.000	-
Hypolipemics	1 (2.7)	22 (59.5)	0.544	-	3 (8.1)	20 (54.1)	1.000	-	3 (8.1)	20 (54.1)	1.000	-
Antihypertensive and cardiovascular risk drugs	3 (8.1)	22 (59.5)	0.537	-	4 (10.8)	21 (56.8)	0.282	-	4 (10.8)	21 (56.8)	0.282	-
Antidiabetics	1 (2.7)	10 (27.0)	1.000	-	2 (5.4)	9 (24.3)	0.567	-	1 (2.7)	10 (27.0)	1.000	-
Type of ART therapy; n (%)												
Two NRTI plus NNRTI	0 (0.0)	7 (18.9)	0.188	-	1 (2.7)	6 (16.2)	0.607	-	0 (0.0)	7 (18.9)	0.428	-
Two NRTI plus b/PI	1 (2.7)	4 (10.8)		-	0 (0.0)	5 (13.5)		-	0 (0.0)	5 (13.5)		-
Two NRTI plus INSTI	0 (0.0)	15 (40.5)		-	1 (2.7)	14 (37.8)		-	3 (8.1)	12 (32.4)		-
Others	2 (5.4)	8 (21.6)		-	2 (5.4)	8 (21.6)		-	1 (2.7)	9 (24.3)		-

Table 2 **Statistical results of the univariate analysis (cont.)**

Respondent characteristics	"I have a good understanding of the reasons I was prescribed each of my medicines" (n=37)		p	OR (95% CI)	"Overall, I am satisfied with my current medicines" (n=37)		p	OR (95% CI)	"I like to be involved in making decisions about my medicines with my doctors" (n=37)		p	OR (95% CI)
	Disagree n (%)	Agree n (%)			Disagree n (%)	Agree n (%)			Disagree n (%)	Agree n (%)		
Therapy type; n (%)												
Triple-therapy	0 (0.0)	27 (73.0)	0.015	1.429 (0.952-2.143)	2 (5.4)	25 (67.6)		-	3 (8.1)	24 (64.9)		-
Monotherapy	3 (8.1)	7 (18.9)			0 (0.0)	2 (5.4)	0.327	-	0 (0.0)	2 (5.4)	0.874	-
Bitherapy					2 (5.4)	6 (16.2)		-	1 (2.7)	7 (18.9)		-
Polymedicated patients (≥6 drugs, including ART)												
N, (%)	2 (5.4)	14 (37.8)	0.568	-	4 (10.8)	12 (32.4)	0.028	1.333 (1.005-1.769)	3 (8.1)	13 (35.1)	0.296	-
Complexity index by MRCI; n (%)												
Low MRCI (< 11)	1 (2.7)	16 (43.2)	1.000	-	0 (0.0)	17 (46.0)	0.109	-	1 (2.7)	16 (43.2)	0.609	-
High MRCI (≥ 11)	2 (5.4)	18 (48.7)		-	4 (10.8)	16 (43.2)		-	3 (8.1)	17 (46.0)		-

OD; Odds ratio, Confidence Interval; CI, NRTI; nucleoside reverse transcriptase inhibitors, NNRTI; non-nucleoside reverse transcriptase inhibitor, b/PI; boosted protease inhibitor, INSTI; integrase strand transfer inhibitor, MRCI; Medication Regimen Complexity Index

In terms of key questions about deprescription, there were a percentage of patients who had a negative opinion regarding these items. This situation could imply a negative attitude towards deprescription because not all patients were receptive to it. In this sense, will be necessary to explain the benefits that deprescription could have for some of the patients [22]. The process of identifying attitudes and beliefs in relation to the deprescription has been evaluated in elderly and polymedicated patients [23]. To our knowledge, no study had evaluated it in OPLWH. In Switzerland, Zechmann *et al.* [23] performed an exploratory analysis that included, among others, questions about deprescribing. The authors observed that 18 of 19 patients fully trusted their general practitioner, 17 of 19 had participated in shared-decision-making processes even before this study, and 8 of 19 perceived polypharmacy as a substantial burden. They identified patient involvement in deprescribing and coordination of care as key issues for deprescribing among older multimorbid patients with polypharmacy.

It is worth highlighting the role of clinical pharmacist in the area of deprescription. Clear examples could be found in the studies of Whitman *et al.* [24], Blanco *et al.* [22] and McNicholl *et al.* [25]. Of all of them, Blanco *et al.* [22] specifically focus on HIV-infected persons and concluded that the deprescribing process shared by professionals and patients definitively would improve management of treatment in this population, and this was what our current article wanted to highlight. In this sense, Cooley *et al.* [26] showed that medication management capabilities in PLWH over 50 years was reduced compared to seronegative patients of the same age range. In this study, OPLWH scored lower on the "Medication Management Test-Revised" and had a higher pill burden.

An interesting aspect to be evaluated was if clinical and demographic characteristics were associated with these attitudes. Unfortunately, the results were not conclusive. There were only statistically significant differences that defined the subgroup of patients with cardiovascular disease as more likely to have a good knowledge of the medications they take. Something similar happened in patients on triple-therapy *vs.* monotherapy or bitherapy, possibly because triple-therapy treatments usually come in a single-tablet regimen. Also, not having central nervous system pathology seemed to be related to being satisfied with the treatment. The same happened for non-polymedicated patients; probably because of they had to take a lower number of medications.

The main limitation of this study could be the small number of patients, which could limit our analysis, and the loss of information intrinsically related to the dichotomization of the

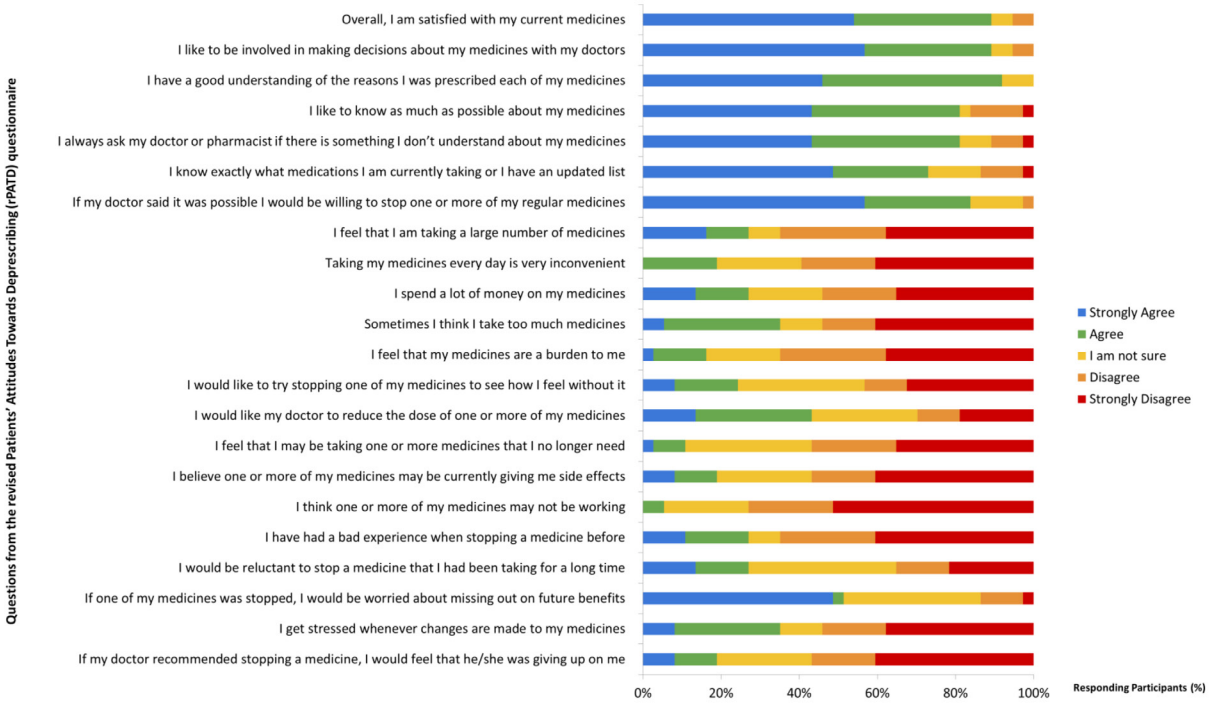

Figure 1 Older VIH+ adults' attitudes toward their medications and deprescribing

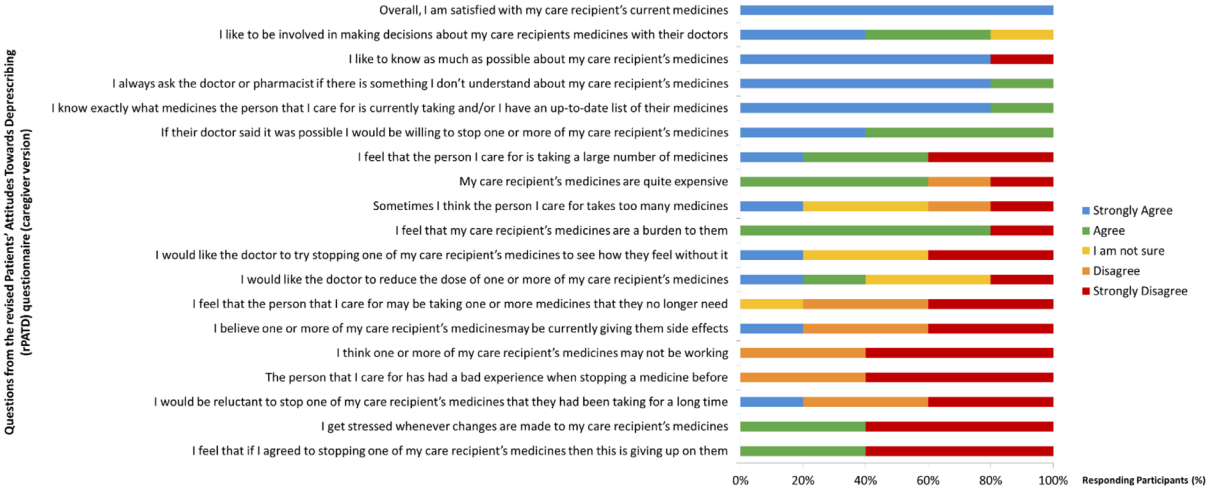

Figure 2 Caregivers' attitudes toward their care medications and deprescribing

indices that were used. However, this was a multicenter study which contained a representative target population. A relevant aspect of our study was the successfully identification of attitudes and believes about the deprescribing concept in OPLWH. We reckoned that HIV-specialist clinical team interventions must be carried out more frequently and intensively in these current patients, with a methodology focused in their needs and individual characteristics but not only on the prescribed medication. This underlines the importance of an effective patient-focused care model to closely monitor high risk-patients. Future efforts would be necessary to validate the most tailored prospective strategies to improve deprescription process.

CONCLUSIONS

This study is the first to explore the beliefs and attitudes of OPWH in relation to deprescription process. There are positive attitudes regarding medication knowledge and many patients who make no effort to take medication. However, there is a percentage of patients who had a negative opinion regarding deprescription. This situation could involve a regressive attitude towards deprescription, as not all patients would be receptive to it. Also, it is important to note that caregivers' responses to questions associated with deprescribing are sometimes very different from those of patients without caregivers. We need to assess in more detail our patients' attitudes towards deprescription, as it helps the process itself to be successful. A more predisposed patient will be able to achieve the pharmacotherapeutic objectives proposed by the healthcare professional in a more efficient way. Thus, we must study and go deeper in our knowledge of techniques that could help us to better understand their preferences, in order to establish effective and successful deprescription strategies.

FUNDING

None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to thank De Juan Roldán JI *et al.* for their work in adapting the Spanish version of the questionnaire.

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/087.2020

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Prevalence of prescription of the Top-10 drug classes to avoid in elderly people living with HIV in a real practice cohort

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Article history
Received: 1 August 2020; Revision Requested: 19 October 2020; Revision Received: 31 October 2020;
Accepted: 13 November 2020; Published: 30 December 2020

ABSTRACT

Objectives. We assessed the prevalence of potentially inappropriate prescriptions (PIP) among older (≥ 65 years) people living with HIV (PLWHIV). Additionally, the secondary objective was to analyse the relationship between pharmacotherapeutic complexity and compliance with STOPP-Beers criteria associated with Top-10 drugs classes to avoid (TOP-10-A) of European AIDS Clinical Society (EACS) guidelines.

Methods. This was a cross-sectional observational single-centre study. PLWHIV aged 65 years-old or over on ART attending at pharmacy outpatient service of Hospital Universitario Virgen de Valme (Sevilla) from December-2019 to March-2020 were included. Patients were classified by age group: 65-69, 70-75 and more than 75 years. Moreover, was analysed the relationship between pharmacotherapeutic complexity and compliance with STOPP-Beers Criteria associated with Top-10-A drugs.

Results. A total of 19 individuals were included. Overall polypharmacy was observed in 16 PLWHIV (84.2%). A PIP included Top-10-A was identified in 9 (47.4%) PLWHIV. Benzodiazepines were the most prevalent group of prescribed drugs in 6 patients (30.0%). Complex patients were observed in 57.9% (MRCI index value greater than 11.25). Similarly, the sum of criteria STOPP-Beers was higher in older patients. Student's t test showed the existence of a statistically significant relationship between pharmacotherapeutic complexity and sum of STOPP-Beers Criteria ($p < 0.05$) in elderly PLWHIV.

Conclusions. Prescription of PIPs is highly prevalent in older PLWHIV. Consistent with data, presence of PIPs were associated a presence of higher pharmacotherapeutic complexity and sum of STOPP-Beers Criteria. The basis for a new revised care plan for PLWHIV focussed on optimising overall patient care pharmacotherapeutic complexity and its possible consequences.

Keywords: HIV; ageing; polypharmacy.

Prevalencia de prescripción del Top-10 clases de fármacos a evitar en pacientes VIH de edad avanzada en una cohorte de práctica clínica real

RESUMEN

Objetivos. Evaluamos la prevalencia de prescripciones potencialmente inapropiadas (PIP) entre las personas mayores (≥ 65 años) que viven con el VIH (PVVIH). Además, el objetivo secundario fue analizar la relación entre la complejidad farmacoterapéutica y el cumplimiento de los criterios STOPP-BEERS asociados con las clases de medicamentos Top-10 para evitar (TOP-10-A) de las directrices de la Sociedad Europea de SIDA Clínica (EACS).

Métodos. Este fue un estudio transversal observacional de un solo centro. Las personas que viven con el VIH de 65 años o más en tratamiento antirretrovírico que asisten al servicio ambulatorio de farmacia del Hospital Universitario Virgen de Valme (Sevilla). Se incluyeron de diciembre de 2019 a marzo de 2020. Los pacientes fueron clasificados por grupo de edad: 65-69, 70-75 y más de 75 años. Además, se analizó la relación entre la complejidad farmacoterapéutica y el cumplimiento de los criterios STOPP-Beers asociados con los medicamentos Top-10-A.

Resultados. Se incluyeron un total de 19 individuos. Se observó polifarmacia general en 16 PVVIH (84,2%). Un PIP incluido Top-10-A fue identificado en 9 (47,4%) PVVS. Las benzodiacepinas fueron el grupo más frecuente de medicamen-

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tos recetados en 6 pacientes (30,0%). Se observaron pacientes complejos en 57,9% (valor del índice MRCI mayor que 11,25). Del mismo modo, la suma de criterios STOPP-Beers fue mayor en pacientes de edad avanzada. Se observó la existencia de una relación estadísticamente significativa entre la complejidad farmacoterapéutica y la suma de los Criterios STOPP-Beers (p <0,05) en PVVIH de edad avanzada.

Conclusiones. La prescripción de PIP es altamente prevalente en las personas que viven con el VIH de mayor edad. De acuerdo con los datos, la presencia de PIP se asoció con una mayor complejidad farmacoterapéutica y la suma de los criterios STOPP-Beers. La base para un nuevo plan de atención revisado para PVVIH se centró en optimizar la complejidad farmacoterapéutica general de la atención al paciente y sus posibles consecuencias.

Palabras clave: VIH; envejecimiento, polifarmacia.

INTRODUCTION

Over the last four decades people living with HIV (PLWHIV) have raised their life expectancy thanks to antiretroviral treatment (ART) [1]. This successful challenge has resulted in clinical services now attending an older HIV-cohort, with patients experiencing many of the problems of an old HIV-negative cohort such as multiple medical diagnoses, comorbidities and frailty [2]. The progressive aging of our patients leads to an increase of polypharmacy, increasing the risk of adverse events, drug interactions and potentially inappropriate prescriptions (PIP) [3].

Annually, the European AIDS Clinical Society (EACS) publishes a scientific guideline whose goal is to provide comprehensive and easily accessible recommendations to clinicians involved in the care of PLWHIV. In 2019, the EACS guideline included for first time a "Selected Top 10 Drug Classes To Avoid (Top-10-A) in elderly PLWHIV" because of the problems they could cause to this population. The list included first generation antihistamines, tricyclic antidepressants, benzodiazepines, atypical antipsychotics, urological spasmolytic agents, stimulant laxatives, nonsteroidal anti-inflammatory drugs, digoxin, long acting sulfonylureas and cold medications [4].

Due to this, one of the most important pending challenges for the future is to adapt a multidisciplinary methodology to the needs of the multidimensional approach needed on PLWHIV, especially those with greater pharmacotherapeutic complexity, who may have a higher risk of non-adherence, hospital readmissions and worse health outcomes. For this reason, it is necessary to incorporate new concepts and strategies of joint work to carry out multidimensional interventions [5-7].

The main objective of this study was to determine the prevalence of prescription drugs included in Top-10-A of the EACS-2019 guideline in PLWHIV elderly patients in a real clinical practice cohort. Additionally, the secondary objective was to analyze the relationship between pharmacotherapeutic complexity and compliance with STOPP-Beers criteria associated with Top-10-A drugs.

METHODS

This was a cross-sectional observational single-center study. PLWHIV aged 65 years-old or over on ART attending at hospital pharmacy outpatient service from December-2019 to March-2020 were included. Those patients received the pharmacotherapeutic follow-up already routinely applied to ambulatory care patients according to a CMO pharmaceutical care model [8]. Patients were excluded if they were participating in a clinical trial or did not give their written informed consent.

The study fulfilled all the ethical requirements and was approved by the Clinical Research Ethics Committee of Sevilla-Sur (code 1420-n-20).

The following variables were analyzed: demographic (age, sex); analytical data, plasma viral load (copies/mL), CD4 cell count (cells/µL); and clinical variables related to comorbidities and pharmacotherapeutics, such as type of ART, concomitant medications, presence of polypharmacy and presence of drugs included in Top-10-A. Only those patients with all variables completed were included in the analysis.

Patients were classified by age group: 65-69, 70-75 and more than 75 years. Data was obtained from the medical record, electronic prescription program, and outpatient dispensing program. Additionally, the secondary objective was to analyze the relationship between pharmacotherapeutic complexity (according to Medication Regimen Complexity Index) [9] and compliance with STOPP-Beers criteria associated with Top-10-A. Moreover, according to Morillo-Verdugo et al. [10] a cut-off value of 11.25 for MRCI index score was employed for considering complex patient. To facilitate the determination of the relationship between MRCI and presence of STOPP-Beers Criteria, the sum of both criteria was performed.

Discrete variables were expressed as counts (percentage) and continuous variables as medians and interquartile ranges (IQRs) or means and standard deviation (SD). An inferential analysis was performed using the T-Student test. The threshold for statistical significance was defined as $p<0.05$. Data analysis was performed using SPSS for Windows 25.0.0 (SPSS, Chicago, IL, USA).

RESULTS

A total of 19 patients were included in this study, mean age of 69.4 ± 5.4 years, 68.4% males. Globally, the number of patients stratified according to the CMO pharmaceutical care model were 12 in level 3 (63.2%), 4 in level 2 (20%) and 3 in level 1 (15.8%). Their demographicaps, clinics, pharmacotherapeutics and pharmaceutical care characteristics were collected in Table 1.

According to the classification groups established by age, the number of patients classified in 65-70 years group were 13, 3 in 70-75 years group and 3 in more than 75 years group. Overall, a number of concomitant drugs was higher in patients more than 75 years (13.1±2.5) compared to 70-75 years (7.6±3) and 65-69 years group (5.7±2.6) ($p=0.001$). Moreover,

Table 1 Baseline demographics, clinics, pharmacotherapeutics and pharmaceutical care characteristics.

	Total cohort N=19
Demographics	
Age (years) Mean ± SD	69.4 ± 5.4
Gender (Male) n (%)	13 (68.4)
CDC classification (aids)	6 (31.6)
Clinics	
CD4 level (> 200 cels/mL)	17 (89.5)
Undetectable viral load (< 50 c/mL)	18 (94.7)
Pharmacotherapeutics	
ART type*	
ITIAN + ITINN	0 (0)
ITIAN + Inin	9 (45.0)
ITIAN + IP	4 (25.0)
Others**	6 (30.0)
Concomitant medication. Mean ± SD	6.8 ± 5.5
Polymedicated n (%)	16 (84.2)
MRCI*** (points). Mean ± SD	11.9 ± 5.8
Pharmaceutical care	
Beers Criteria. Median (IQR)	1 (0-6)
STOPP Criteria. Median (IQR)	1 (0-3)
Stratification ****[a]	
N3	12 (63.2)
N2	4 (20)
N1	3 (15.8)

*ART. Antiretroviral therapy; **Others include all ART regimens without ITIAN; ***MRCI denotes medication regimen complexity Index; ****Stratification according Spanish Society of Hospital Pharmacy.

[a] Distribution of MRCI according to stratification [N3, 9.8 ± 4.6; N2, 15.1 ± 4.1; N1, 19.6 ± 6.4; ANOVA $P_{intergroups}$ <0.001]

9 of the 19 patients (47.4%) had medication included in the Top-10-A. Benzodiazepines were the most prevalent group of prescribed drugs included in 6 patients (30.0%), followed by nonsteroidal anti-inflammatory drugs (11.1%), urological spasmolytic agents (5.6%), digoxin (5.6%) and first generation antihistamines (5.6%).

Regarding one of the main variables, the MRCI index mean was 11.9±5.8, complex patients in 57.9% (MRCI index value greater than 11.25). Additionally, MRCI index was higher for patients classified in more than 75 years group (22.8±2.1) compared to 70-75 years (14.7±6.5) and 65-70 years group (9.9±3.4) (p=0.003). The other main variable includes the sum of STOPP-Beers criteria. As in the MRCI value, the sum of the criteria was higher for patients of higher age group: patients >75 years (4.4±2.1), 70-75 years (3.2±2.6) and 65-69 years (2.1±1.7) (p<0.001). Figure 1 shows the relationship of the MRCI value and sum of STOPP-Beers criteria by age group and the results of statistical test.

More than 50% of these criteria were associated with the prescription of drugs included Top-10-A, fundamentally benzodiazepines.

DISCUSSION

In the present study, we found a high overall frequency of prescription of the drugs included in Top-10-A in our population. Moreover, high MRCI values in older people with HIV are related to an increased presence of STOPP-Beers Criteria. Finally, the statistical relationship shows how there is a greater sum of the values of the STOPP-Beers criteria as the MRCI values increase.

To our knowledge, this is the first study that clearly correlates pharmacotherapeutic complexity with presence of STOPP-Beers criteria in elderly PLWHIV. Previous studies observed that HIV-infected older adults were polymedicated, where more than 50% were PIP, including Top-10-A drugs [11]. Furthermore, Tseng et al. [12] showed the association between aging and polypharmacy with the consequent increase in the risk of interactions with ART, particularly cardiovascular agents such as digoxin, included in Top-10-A. Because of polypharmacy is associated with increase in drug-related morbidity and mortality from adverse events and drug interactions, identifying patients with polypharmacy is relevant. In addition, identifying patients with PIP is important due to an increased risk of drug interactions by 85.0% [13].

A serie of tools used to detect and prevent the use of PIP among older adults of the general population include the Beers criteria for inappropriate medication use in older adults [14] and Screening Tool of Older Persons' Prescription (STOPP) [11]. Due to patient aging, there is an increasing percentage of polymedicated patients with the inherent risks already mentioned, which has increased interest in this area. McNicholl et al. [15] showed a statistically significant relationship between polypharmacy and the presence of STOPP-Beers criteria. However, the concept of polypharmacy only takes into account the number of prescribed medication without considering the complexity of the pharmacotherapeutic regimen. For this reason, we have used the MRCI index, which is a validated tool that evaluates treatment regimen complexity based on the number of medications, dosage form, dosage frequency, and additional or special instructions. This tool allows us to know the impact of the pharmacotherapeutic regimen and its possible relationship with the development of drug-drug interactions and adverse events described in STOPP-Beers criteria.

Despite the statistically significant results, we proposed as a proof of concept study to demonstrate the importance of polypharmacy in older PLWHIV. It is a good initial approach for this problem, but due to the need to face this

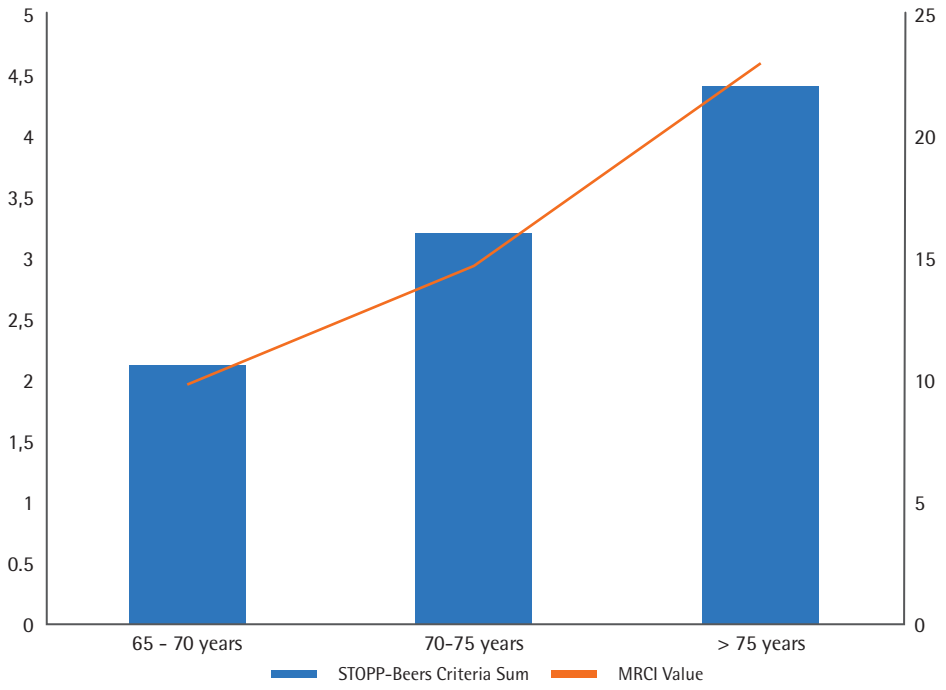

Figure 1 | **Relationship of the MRCI value and sum of STOPP-Beers criteria by age group.The analysis using Student's T test showed the existence of statistically significant relationship between variables (p<0.05).**

challenge, a multicenter study is being carried out to obtain results that facilitate the development of strategies, such as deprescription, to improve the pharmacotherapeutic strategies of PLWHIV.

The present study may have some limitations. First, our study was based on a single urban safety net hospital, so generalizability to other settings and patient population would be a priority. Moreover, the sample size was reduced and this makes the results may not apply to hospitals. On the other hand, STOPP-Beers criteria were validated to patients ≥ 65 years non HIV-infected. Despite these potential limitations, this study has successfully identified the correlation between MRCI and these criteria. HIV specialist interventions should be carried out more frequently and intensively in current patients, with a methodology that takes into account their needs and individual characteristics and not focused on the prescribed medication, stressing the importance of an effective patient care model to closely monitor high risk-patients.

In conclusion, the results of our study form the basis for a new revised care plan for PLWHIV focused on optimising overall patient care, not only limited to viral load goal achievement but also in their pharmacotherapeutic complexity and its possible consequences. No doubt, not only multidisciplinary, but also multidimensionally would be the most successful to approach PLWHIV in the near future.

FUNDING

None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/091.2020

COVID-19 and Acute Respiratory Distress Syndrome. Impact of corticosteroid treatment and predictors of poor outcome

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Article history
Received: 9 August 2020; Revision Requested: 29 September 2020; Revision Received: 1 October 2020; Accepted: 6 October 2020; Published: 15 December 2020

ABSTRACT

Objectives. To assess the impact of corticosteroids on inflammatory and respiratory parameters of patients with COVID-19 and acute respiratory distress syndrome (ARDS).

Methods. Longitudinal, retrospective, observational study conducted in an ICU of a second level hospital. Adult patients with COVID-19 were included. Baseline characteristics, data on SARS-CoV-2 infection, treatment received, evolution of respiratory and inflammatory parameters, and ICU and hospital stay and mortality were analyzed.

Results. A total of 27 patients were included, 63% men, median age: 68.4 (51.8, 72.2) years. All patients met ARDS criteria and received MV and corticosteroids. After corticosteroids treatment we observed a reduction in the O_2 A-a gradient [day 0: 322 (249, 425); day 3: 169 (129.5, 239.5) p<0.001; day 5: 144 (127.5, 228.0) p<0.001; day 7: 192 (120, 261) p=0.002] and an increase in the pO_2/FiO_2 ratio on days 3 and 5, but not on day 7 [day 0: 129 (100, 168); day 3: 193 (140, 236) p=0.002; day 5: 183 (141, 255) p=0.004; day 7: 170 (116, 251) p=0.057]. CRP also decreased on days 3 and 5 and increased again on day 7 [day 0: 16 (8.6, 24); day 3: 3.4 (1.7, 10.2) p<0.001; day 5: 4.1 (1.4, 10.2) p<0.001; day 7: 13.5 (6.8, 17.3) p=0.063]. Persistence of moderate ARDS on day 7 was related to a greater risk of poor outcome (OR 6.417 [1.091-37.735], p=0.040)

Conclusion. Corticosteroids appears to reduce the inflammation and temporarily improve the oxygenation in COVID-19 and ARDS patients. Persistence of ARDS after 7 days treatment is a predictor of poor outcome.

Key words: COVID-19, ARDS, mechanical ventilation, corticosteroids, ICU

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COVID-19 y Síndrome de Distress Respiratorio Agudo. Impacto del tratamiento con corticoides y predictores de mal pronóstico

RESUMEN

Objetivos. Evaluar el impacto del tratamiento con corticoides en los parámetros inflamatorios y respiratorios de los pacientes con Síndrome de Dificultad Respiratoria Aguda (SDRA) secundario a COVID-19

Métodos. Estudio longitudinal, retrospectivo, observacional en una UCI de un hospital de segundo nivel. Se incluyeron los pacientes adultos ingresados en UCI por COVID-19. Analizamos características basales, datos de la infección por SARS-CoV-2, tratamiento recibido, evolución de los parámetros respiratorios e inflamatorios y estancia y mortalidad en UCI y hospitalaria.

Resultados. 27 pacientes, 63% hombres, mediana de edad: 68.4 (51.8, 72.2) años. Todos recibieron ventilación mecánica y cumplieron criterios de SDRA. Todos recibieron corticoides. Tras la administración de corticoides observamos una reducción del gradiente A-a de O_2 [día 0: 322 (249, 425); día 3: 169 (129.5, 239.5) p<0.001; día 5: 144 (127.5, 228.0) p<0.001; día 7: 192 (120, 261) p=0.002] y un aumento en la relación pO_2/FiO_2 en los días 3 y 5, pero no al día 7 [día 0: 129 (100, 168); día 3: 193 (140, 236) p=0.002; día 5: 183 (141, 255) p=0.004; día 7: 170 (116, 251) p=0.057]. La PCR descendió a los días 3 y 5 volviendo a subir al día 7 [día 0: 16 (8.6, 24); día 3: 3.4 (1.7, 10.2) p<0.001; día 5: 4.1 (1.4, 10.2) p<0.001; día 7: 13.5 (6.8, 17.3) p=0.063]. La persistencia de SDRA moderado al día 7 se relacionó con un peor pronóstico (OR 6.417 [1.091-37.735], p=0.040)

Conclusión. Los corticosteroides parecen reducir la inflamación y mejorar temporalmente la oxigenación en pacientes con SDRA y COVID-19. La persistencia de SDRA moderado tras 7 días de tratamiento es un predictor de mal pronóstico.

Palabras clave: COVID-19, SDRA, ventilación mecánica, UCI, corticosteroides, ICU

INTRODUCTION

On 11 March 2020 the World Health Organization announced that the outbreak of the disease caused by coronavirus SARS-CoV-2 (*severe acute syndrome coronavirus 2*), known as COVID-19, can be characterized as a pandemic, after having first appeared in late 2019 in China.

COVID-19 has been a challenge for health systems all over the world; especially for ICUs that have had to expand to assume a number of patients that exceeded the number of beds available. At the same time, the lack of a known, effective treatment has led to a spate of treatment recommendations [1–4], which are not always backed by sufficient scientific evidence [5].

It has been suggested that the clinical course of COVID-19 evolves over several phases. The initial phase would be marked by a high viral load. The subsequent inflammatory response (evaluated by means of determination of interleukins but also estimated using C reactive protein [CRP], lactate dehydrogenase [LDH], D-dimer, ferritin, etc.) would be the cause of clinical worsening in some patients [6] This theory has not been confirmed and other researchers have cast doubt about the existence and importance of the "cytokine storm"[7].

According to this theory, different treatments targeted at modulating the inflammatory response, including corticosteroids, have been suggested. In a retrospective analysis of 84 patients with COVID-19 and ARDS (treated at one hospital in Wuhan) lower mortality was observed in those patients who had received methylprednisolone (HR 0.38; 95% CI 0.20-0.72) [8]. The recommendation to administer corticosteroids early during moderate-severe ARDS [9] carries more weight after publication of the results of a randomized clinical trial in which dexamethasone was shown to reduce the duration of mechanical ventilation (MV) and the mortality, compared to routine intensive care [10]. Data also exist that suggest a benefit of corticosteroid treatment in patients with community-acquired pneumonia and an intense inflammatory response [11] and, even, in patients with influenza-related pneumonia and ARDS [12]. However, unfavorable results have been notified in patients with respiratory infections of viral etiology, such as MERS (Middle East Respiratory Syndrome) [13] and also in influenza-related pneumonia [14, 15], which means we must be circumspect with its administration [16].

The Surviving Sepsis Campaign suggests using systemic corticosteroids in patients subjected to MV and ARDS following COVID-19 [2].

Recently, results of RECOVERY clinical trial have showed that use of dexamethasone resulted in lower 28-day mortality among COVID-19 patients who were receiving invasive mechanical ventilation [17].

The main objective of our study is to analyze the effects of a short course of corticosteroids on the respiratory and inflammatory parameters of patients undergoing MV because of ARDS following COVID-19. Our secondary objective is to identify predictors of poor outcome (death or prolonged MV).

MATERIAL AND METHODS

Scope of study. A second level Spanish hospital ICU with 22 beds (14 of which are suitable for patients on MV). Patients received treatment in accordance with our center's protocol, which included a recommendation for methylprednisolone (0.5 mg/kg/12 hours, 3 days) if the patient was receiving MV and complied with ARDS criteria [18]. Our protocol recommended performing a control PCR for SARS-CoV-2 10 days from admission (if the patient had no fever); in the event of a positive result a new test at 5 days was recommended.

Study period. Patients admitted during the first wave of the COVID-19 pandemic (March-June 2020).

Study design. Longitudinal, retrospective, observational study.

Inclusion criteria. Adult patients admitted to the ICU because of respiratory failure secondary to COVID-19, diagnosed by a positive PCR for SARS-CoV-2.

Exclusion criteria. Not applicable.

Ethical aspects. The study was approved by the Galicia Ethics Committee for Research into Medicines (CEIm-G) (code 2020/246).

Measures. We assessed sociodemographic data (age and sex), comorbidities, data on SARS-CoV-2 infection (duration of the disease at admission, time until a negative PCR test for SARS-CoV-2), severity scores at admission (SOFA and APACHE II), treatments received, respiratory support, evolution of respiratory and inflammatory parameters during the first week of MV and duration of the MV and ICU and hospital stay; in addition to the incidence of coinfections at admission and superinfections during stay in the ICU (defined by positive cultures and/or significant elevation in procalcitonin: ≥0.5 ng/mL).

Comorbidities were recorded according to the data obtained from the clinical history. They were grouped according to the system affected: cardiovascular (history of ischemic cardiopathy, heart failure or severe valvular disease), respiratory (diagnosis of COPD or asthma), central nervous system (history of cerebrovascular disease with or without sequelae), and liver (cirrhosis at any stage). Hematologic malignancy included those patients with a history of any kind of leukemia or lymphoma, regardless of time from diagnosis. Cancer included those patients who had received treatment for their neoplasia in the last 5 years.

Patients who needed MV for 21 days or less were classified as Group A (*good outcome*). Patients who died or needed MV for more than 21 days were classified as Grupo B (*poor outcome*).

The main objective was to analyze evolution of respiratory (pO_2/FiO_2 ratio and O_2 alveolo-arterial gradient) and inflammatory parameters (CRP, LDH, D-dimer, ferritin, lymphocyte count) after administration of corticosteroids. To homogenize our data, we used arterial blood gas results obtained daily while the patient was in supine position. We consider resolution of moderate ARDS when the pO_2/FiO_2 ratio remained above 200 for at least 48 hours.

Our secondary objective was to identify the variables present at admission or during the first week under MV that predict a poor outcome (death or need for MV for more than 21 days). We evaluated the existence of a relationship between the poor result and the main inflammatory and respiratory parameters, viral persistence and the presence of coinfection upon admission to the ICU.

Statistical analysis. Continuous variables are shown as median and p25, p75; qualitative variables are shown as number and percentage. To compare medians, we used the Mann-Whitney U test, and we compared percentages using the chi-squared test. We used logistic regression to assess the relationship between the risk of poor outcome and the variables selected. We have assumed an α error of 0.05. We used the statistical software package IBM SPSS Statistics, Version 19.0 (IBM Corp., Armonk, NY, USA) for statistical analysis and to plot graphs.

RESULTS

Up to June 16, 2020, 27 patients were admitted to our center's COVID-ICU. 63% were men and their median age was 68.4 (51.8, 72.2) years. Comorbidities and basal characteristics of patients are shown in Table 1.

Figure 1 summarizes both MV and ICU and hospital stay times for each patient.

Patients were admitted to the ICU after spending a median of 3 (1, 4) days on the hospital; 4 (2.2, 7.7) days in Group A (0, 3) and 2 (0, 3) days in Group B, (p=0.047). Both antiviral and anti-inflammatory treatment received by patients are summarized in Table 2.

All patients received MV and 15 patients (55.5%) received non-invasive ventilation (NIV) prior to onset of MV. Parameters related to respiratory support are shown in Table 3.

Ferritin levels at the time of onset of MV were 548 (280.5, 1970.5) mg/mL, 282 (220, 2281) in Group A and 1151 (496.2, 2108.2) in Group B (p=0.242).

A total of 12 (44.4%) patients presented a positive control SARS-CoV-2 PCR; 7 (58.3%) patients in Group A and 5 (33.3%) patients in Group B (p=*0.194*). 6 (22.2%) patients presented two positive control SARS-CoV-2 PCR; 4 (33.3%) patients in Group A and 2 (13.3%) patients in Group B (p=*0.214*), and four patients did not have a negative control PCR before leaving hospital (14.8%), 3 (25%) patients in Group A and 1 (6.7) patient in Group B (p=0.183).

A total of 27 patients (100%) complied with ARDS criteria at the time of starting MV and received treatment with 0.5 mg/kg/12h of methylprednisolone. Treatment lasted 3 (3, 4) days, with a median of 3 (2, 4) in Group A patients and 3 (3, 4.2) in Group B patients (p=0.294).

Corticosteroids was started at the same time as mechanical ventilation in 26 patients (96,3%). Figure 2 shows the evolution of inflammatory and respiratory parameters from starting corticosteroid treatment to day 28, and Table 4 shows the comparison of baseline values with those measured on days 3, 5 and 7 after starting corticosteroids. We have not made comparisons beyond the seventh day due to the small number of patients and high variability, which is probably related to the presence or absence of complications, especially infectious complications.

Figure 3 shows the evolution of inflammatory and respiratory parameters in group A and group B patients. In table 5 we compare those parameters in group A and group B patients on admission and on days 3, 5 and 7, in order to explore early differences between the two groups.

When we searched for factors that predict poor outcome (death or need for prolonged MV) during the first week of MV, we found that only moderate ARDS criteria persisting 7 days from MV onset predicts a poor outcome (OR: 6.417, 95% CI 1.091-37.735, p=0.040) (Table 6).

DISCUSSION

In this study we describe 27 patients admitted to our ICU because of COVID-19 from March to June 2020. A total of 1880 cases were diagnosed in our healthcare area up to June 16 (approximate incidence of 652 cases per 100,000 inhabitants); of these 132 died (7.0%). ICU admission represents 1.4% of all cases diagnosed and 5.1% of COVID-19-related hospital admissions. The percentage of patients admitted to the ICU is far from the 11.3% reported by Rodríguez et al. [19], although close to the 7% published by Yang et al [20].

The sample is a predominantly male population with few comorbidities. Our data are similar to other series published on critically ill COVID-19 patients, although the median age and percentage of patients with onco-hematologic diseases is slightly higher in our study [19–26].

The role of NIV in these patients has been a moot point during the pandemic; both because of the high rate of failure and the risk of infecting healthcare staff. In over half our patients (55.6%) NIV was tested and failed; MV was required in 100% of patients. Other authors have reported high levels of failure of NIV: 85.2% in the Tarragona study [19]. In the Lombardy and Washington series barely 11% and 19% respectively only received NIV, while the number of patients receiving MV after having received NIV is not specified [25] and Hua et al. report 32.5% of patients treated with NIV. None of the studies published to date attain 100% of patients under MV. However, the Vitoria study exceeds 90% [22] and both the Lombardy and Tarragona studies are close (88% and 86%, respectively) [19, 25]. At the other extreme, just 24% of patients from the Hua et al. series and 42% of the Yang et al. series received MV [20, 26].

The severity of respiratory failure is notable (median pO_2/FiO_2 ratio of 129, and O_2 A-a gradient of 322 mmHg O_2, at MV onset) with a high percentage of patients meeting moderate (88.9%) and severe (25.9%) ARDS criteria. Only Yang et al. have observed a lower pO_2/FiO_2 ratio, however, they report that only 67% of patients comply with ARDS criteria and just 42% of their patients

Table 1 Comorbidities, basal characteristics, evolution and results

	Overall	Group A	Group B	p
n	27	12	15	
Male sex	17 (63)	7 (58.3)	10 (66.7)	0.656
Age	68.4 (51.8, 72.2)	60.1 (45.2, 71.9)	70.8 (58.7, 72.9)	0.841
Comorbidities				
Arterial hypertension	11 (40.7)	6 (50)	5 (33.3)	0.381
Dyslipidemia	11 (40.7)	5 (41.7)	6 (40)	0.930
Diabetes mellitus	5 (18.5)	1 (8.3)	4 (26.7)	0.223
Cardiovascular	1 (3.7)	1 (8.3)	0	0.255
Respiratory	5 (18.5)	1 (8.3)	4 (26.7)	0.233
CNS	1 (3.7)	0	1 (6.7)	0.362
Liver	2 (7.4)	1 (8.3)	1 (6.7)	0.869
Hematologic malignancy	2 (7.4)	2 (16.7)	0	0,100
Cancer	3 (11.1)	2 (16.7)	1 (6.7)	0.411
BMI	28.5 (25.2, 32.6)	29.0 (25.5, 34.2)	27.4 (25.2, 31.3)	0.902
Disease course and duration				
Ss-H admission (d)	7.0 (3.5, 9.0)	5 (2, 8)	7 (4.75, 10)	0.798
Ss-ICU admission (d)	10 (7.0, 12.5)	10 (9, 12)	9.5 (7, 13.2)	0.063
Ss-MV onset (d)	12 (9, 14)	12 (10, 13)	11.5 (8.5, 14.2)	0.056
Days PCR + until PCR -	21 (16, 29)	21 (10.5, 38.5)	22.5 (18.5, 27.5)	0.419
Symptoms until PCR - (d)	33 (28, 36)	34.5 (21.7, 46.2)	31 (28, 36)	0.943
Severity scores				
APACHE II	14 (10, 17)	14 (9.2, 17.7)	14 (11, 17)	0.580
SOFA 24 h	4 (4, 7)	5.5 (4, 6.7)	4 (4, 7)	0.092
Oxygenation parameters at the onset of mechanical ventilation				
$pO_2/FiO_2 < 300$	27 (100)			
$pO_2/FiO_2 < 200$	24 (88.9)	10 (83.3)	14 (93.3)	0.411
$pO_2/FiO_2 < 100$	7 (25.9)	3 (25)	4 (26.7)	0.922
Coinfection and superinfection in the ICU				
Coinfection	13 (48.1)	5 (41.7)	8 (53.3)	0.547
Superinfection	18 (66.7)	4 (33.3)	14 (93.3)	0.001
MV onset-superinfec (d)	14 (8.7, 22.2)	10.5 (8.5, 11)	17 (8.7, 23.5)	0.151
Results				
Deceased at 28 d	2 (7.4)	0 (0)	2 (13.3)	0.189
Under MV at 28 d	10 (37)	0	10 (66.7)	<0.001
ICU at 28 d	12 (44.4)	0	12 (80)	<0.001
Hospital ward at 28 d	12 (44.4)	11 (91.7)	1 (6.7)	<0.001
Home at 28 d	1 (3.7)	1 (8.3)	0	0.255
ICU mortality	3 (11.1)	0	3 (21.4)	0.088
ICU LOS	26 (19, 39)	19 (10.2, 23.5)	35 (28, 45)	<0.001
Hospital LOS	47 (35, 54)	41 (35.7, 47.5)	53 (35, 58)	0.067

CNS: central nervous system, BMI: body mass index, Ss: symptoms, H: hospital, MV: mechanical ventilation, d: days, LOS: length of stay.

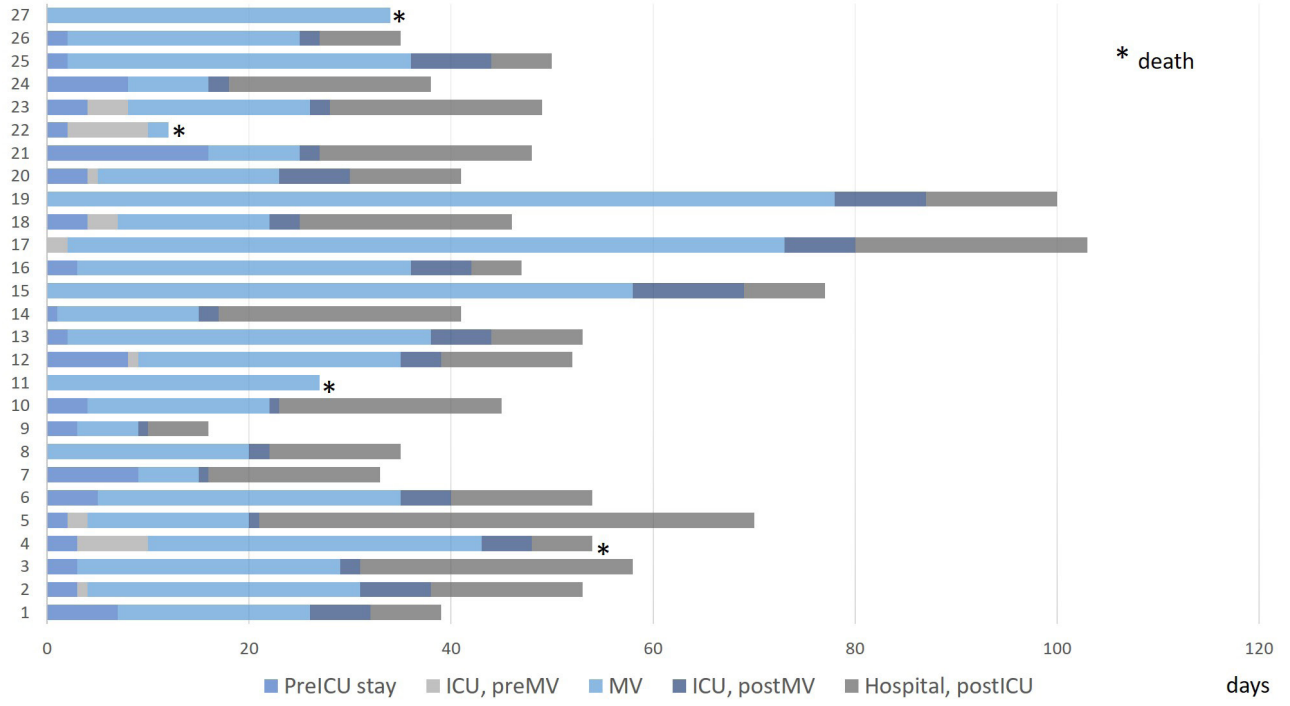

Figure 1 | **Mechanical ventilation and ICU and hospital stay times for each patient (MV: mechanical ventilation; ICU: intensive care unit)**

Table 2 | **Treatment received**

	Overall	Group A	Group B	p
Lopinavir-ritonavir	20 (74.1)	10 (83.3)	10 (66.7)	0.326
Interferon ß-1b	11 (40.7)	6 (50)	5 (33.3)	0.381
Corticosteroid bolus (preICU)	6 (22.2)	2 (16.7)	4 (26.7)	0.535
Tocilizumab (preICU)	3 (11.1)	2 (16.7)	1 (6.7)	0.411
Tocilizumab (in ICU)	8 (29.6)	0	8 (53.3%)	0.003
Hydroxychloroquine	27 (100)			
Methylprednisolone	27 (100)			
Days methylprednisolone	3 (3, 4)	3 (2, 4)	3 (3, 4.2)	0.294
Antibiotic	27 (100)			

receive MV. For the remaining series, the pO_2/FiO_2 ratio at the onset of MV varies between 130 and 169, and incidence of ARDS is around 70%. In our series, 55% of patients continue to comply with moderate ARDS criteria after 7 days under MV. Median time until a pO_2/FiO_2 ratio above of 200 is 9 days. The severity of respiratory failure of our patients is also reflected in the percentage of patients requiring ventilation in prone position (96.3%), in the high number of sessions they received, with a median of 7, and the duration of MV (median 23 days); only the Blake et al. and Rodríguez et al. series are close, with 79% and 82%, respectively, of patients that receive ventilation in prone position. The remaining series vary between 11.5% [20] and 50% [22,23].

Contrary to the severity of respiratory failure, we have barely observed other cases of organ failure, as reflected in the median SOFA score: 4 (4, 7). Both the Vitoria and Tarragona studies reported a higher score (7 and 6, respectively) [19,22] and Yang et al. published an incidence of renal failure and liver dysfunction of 29% [20].

Table 3 Respiratory therapy

	Overall	Group A	Group B	p
NIV	15 (55.6)	8 (66.7)	7 (46.7)	0.299
Days NIV	1 (0, 3)	0.5 (0, 2.7)	1 (0, 7)	0.435
MV	27 (100)			
Days MV	23 (15, 33)	15.5 (8.2, 18)	33 (26, 36)	<0.001
Prone ventilation	26 (96.3)	11 (91.7)	15 (100)	0.255
Prone vent sessions	7 (4.7, 9.2)	6 (3, 8)	7 (5, 17)	0.076
pO_2/FiO_2 < 200 at 7 d	15 (55.5)	4 (36.4)	11 (78.6)	0.032
Days moderate ARDS	9 (4, 16)	5 (2.2, 12.7)	15 (9, 21)	0.014
Tracheotomy	12 (44.4)	0	12 (80)	<0.01

NIV: non-invasive respiratory support, MV: mechanical ventilation, d: days

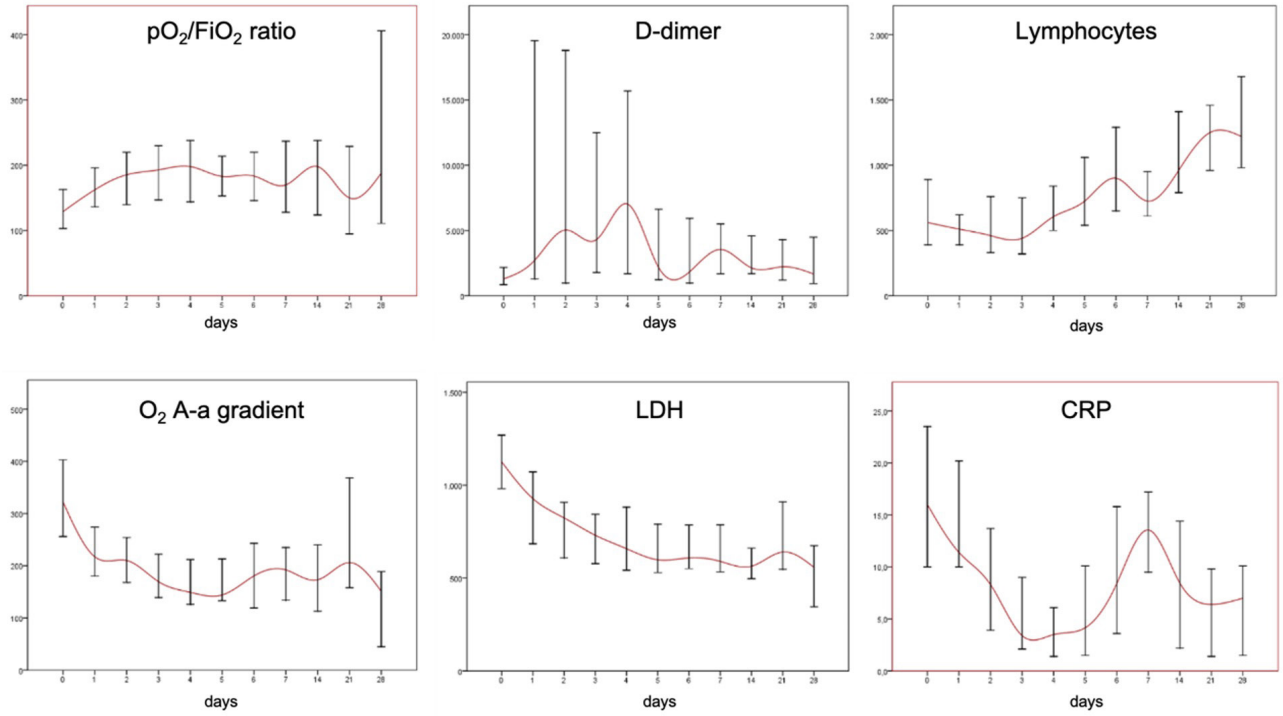

Figure 2 Evolution of inflammatory and respiratory parameters from starting corticosteroid treatment: D-dimer (ng/mL); LDH, lactate dehydrogenase, U/L); Lymphocytes count, cells/mL); CRP, C-reactive protein, mg/dL); O_2 A-a gradient, mmHg; pO_2/FiO_2 ratio

Barrasa et al. and Rodríguez et al. [19,22] reviewed treatments administered to their patients. In both studies and ours, treatment most commonly administered were hydroxychloroquine (>90%) and lopinavir-ritonavir (74.1% in our case, above the 90% in the other two series). Less homogeneous is the interferon β-1B treatment, received by less than 50% of patients from Rodríguez et al's. study and ours, and 85% of patients from the Barrasa et al. series; and tocilizumab treatment (40.7% in our study, less than 5% in the other two). All our patients received corticosteroids after onset of MV, as opposed to 35% of the Vitoria et al. study, 2.3% of the Tarragona study, and 58% of patients from the Yang et al. study [19, 20, 22].

When attempting to evaluate the impact of the treatment with corticosteroids, we observed a significant reduction in

Table 4 Evolution of respiratory and inflammatory parameters

		Day 0	Day 3	Day 5	Day 7
D-dimer (ng/mL)	Value	1290 (843, 2865.5)	4308 (1776, 12485)	2166.5 (1228.2, 8281.2)	3541 (1673, 5507)
	p (compared to day 0)		0.067	0.096	0.033
LDH (U/L)	Value	1126 (817.5, 1361)	730.5 (542, 871.7)	598.5 (528.2, 793.5)	590.0 (525.5, 800)
	p (compared to day 0)		<0.001	<0.001	<0.001
Lymphs count (cells/mL)	Value	560 (380, 900)	440 (315, 800)	725 (518.7, 1182.5)	725 (540.9, 1122.5)
	p (compared to day 0)		0.296	0.078	0.031
CRP (mg/dL)	Value	16 (8.6, 24.0)	3.4 (1.7, 10.2)	4.1 (1.4, 10.2)	13.5 (6.8, 17.3)
	p (compared to day 0)		<0.001	<0.001	0.063
O_2 A-a grad (mmHg)	Value	322 (249, 425)	169 (129.5, 239.5)	144 (127.5, 228.0)	192 (120, 261)
	p (compared to day 0)		<0.001	<0.001	0.002
pO_2/FiO_2	Value	129 (100, 168)	193 (140, 236)	183 (141, 255)	170 (116, 251)
	p (compared to day 0)		0.002	0.004	0.057

LDH: lactate dehydrogenase, lymphs: lymphocytes, CRP: C reactive protein, grad: gradient

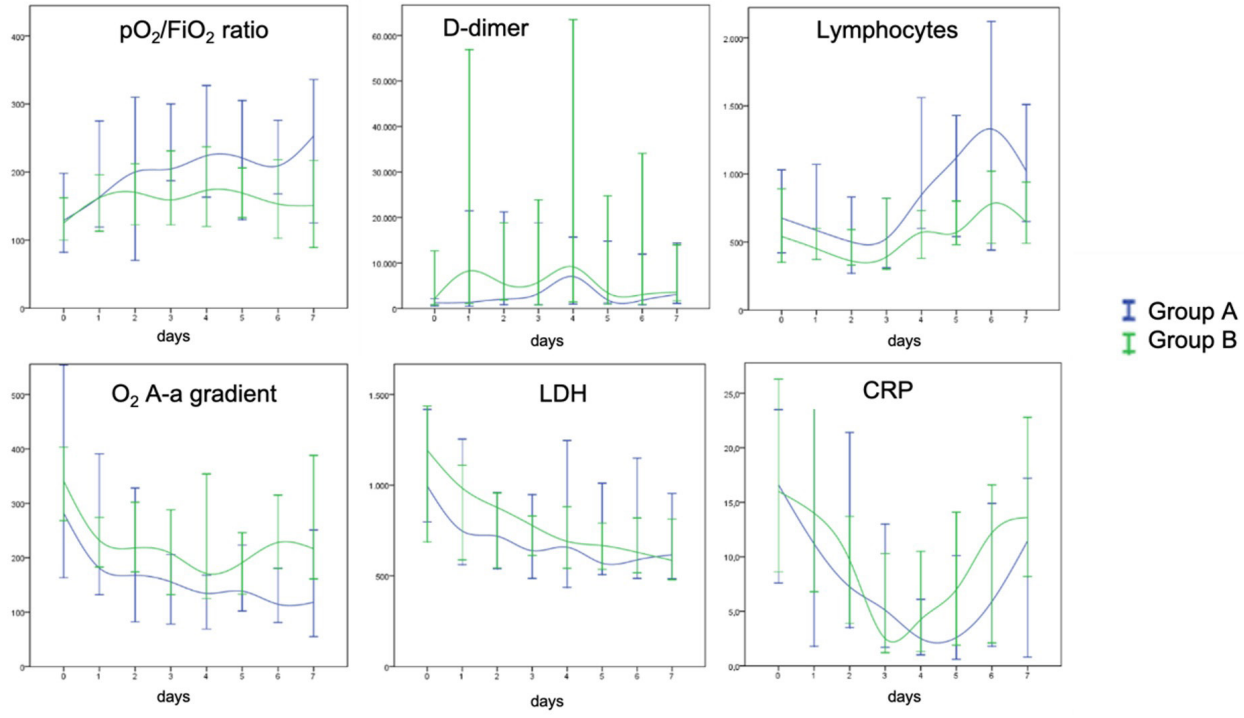

Figure 3 Evolution of inflammatory and respiratory parameters in group A and group B patients: D-dimer (ng/mL); LDH, lactate dehydrogenase, U/L); Lymphocytes count, cells/mL); CRP, C-reactive protein, mg/dL); O_2 A-a gradient, mmHg; pO_2/FiO_2 ratio

Table 5 Comparison of the evolution in respiratory and inflammatory parameters between Group A and B

		Day 0	Day 3	Day 5	Day 7
D-dimer	Group A	1290	3321	1874	3082
(ng/mL)		(663, 2028)	(1806, 9177)	(1228.2, 13631.7)	(1226.7, 5503.2)
	Group B	2797	9144	3435	3541
		(862, 10437)	(1504.5, 21219.7)	(1217.7, 4741)	(1788, 11450)
	p	0.099	0.462	1	0.563
O_2 A-a	Group A	282	155.5	138.5	118
grad		(166.7, 521.7)	(83.5, 205.5)	(103.2, 208.5)	(70, 225)
	Group B	341	191	191	216.5
		(268, 403)	(136.5, 239.5)	(136.5, 239.5)	(170, 340)
	p	0.626	0.190	0.157	0.006
LDH	Group A	995.5	638.5	569.5	616
(U/L)		(804.5, 1363.5)	(497, 941.2)	(511.7, 959.2)	(522.2, 943.5)
	Group B	1205	778	667	585
		(1019, 1345)	(618, 820.2)	(557, 785.5)	(518, 787)
	p	0.495	0.954	0.644	0.439
Lymphs count	Group A	675	525	1120	1020
(cells/mL)		(427.5, 997.5)	(312.5, 810)	(590, 1420)	(665, 1440)
	Group B	540	390	570	645
		(350, 890)	(310, 785)	(506.2, 762.5)	(497.5, 880)
	p	0.421	0.785	0.040	0.051
pO_2/FiO_2	Group A	129	204.5	220.5	253
		(87.5, 191.5)	(189.7, 290)	(135, 296.2)	(145.332)
	Group B	125	159	169	150.5
		(100, 162)	(125, 227.2)	(143, 205.5)	(97.2, 187.7)
	p	0.660	0.051	0.211	0.027
CRP	Group A	16.6	5.1	2.6	11.4
(mg/dL)		(8.2, 22.9)	(2, 12.3)	(1.2, 9)	(1.2, 16.6)
	Group B	16	2.5	7	13.6
		(8.6, 26.3)	(1.5, 9)	(2, 13.6)	(9.5, 21.1)
	p	0.626	0.498	0.224	0.190

Grad: gradient, LDH: lactate dehydrogenase, lymphs: lymphocytes, CRP: C reactive protein

LDH, CRP and O_2 A-a gradient, in addition to an increase in pO_2/FiO_2 ratio. CRP levels decreased initially and went up again once methylprednisolone treatment ended. No statistically significant differences between median CRP on day 7 and at onset of treatment were detected. The pO_2/FiO_2 ratio also increased initially and then reduced until there were no statistically significant differences between days 0 and 7 of MV. These trends appear to coincide with the time when patients received methylprednisolone; given the results of clinical trials with lopinavir-ritonavir and hydroxychloroquine [27–29], it does not appear that this effect can be attributed to the remaining treatments received by our patients. On the other hand, the initial favorable course with subsequent worsening leads us to suspect that this is not natural disease course, but rather can be impacted by the administration of methylprednisolone. Wu et al. observed that patients with COVID-19 and ARDS who had received methylprednisolone presented longer survival [8], and preliminary results of RECOVERY trial show that low doses of dexamethasone reduce the mortality of COVID-19 patients that require respiratory support, especially MV [17]

Table 6 Poor outcome predictors. Univariate analysis

	OR	CI	p
Positive control PCR	2.8	0.582-13.478	0.199
Positive control PCR x 2	3.25	0,480-21,997	0.227
Coinfection on admission	1.6	0.346-7.401	0.548
Severe ARDS day 0 MV	2.8	0.222-35.288	0.426
Moderate ARDS day 0 MV	1.091	0.192-6.196	0,922
Moderate ARDS day 7 MV	6.417	1.091-37.735	0.040
CRP > 10 mg/dL day 0 MV	1.375	0.262-7.220	0.707
CRP > 10 mg/dL day 7 MV	1.429	0.297-6.977	0.656
< 500 lymphocytes day 0 MV	1.225	0.265-5.667	0.795
< 500 lymphocytes day 7 MV	3	0.269-33.487	0.372

ARDS: acute respiratory distress syndrome, MV: mechanical ventilation, CRP: C reactive protein

One differentiating aspect of our series is the high incidence of co-infection at ICU admission (48.1%). Following our protocol, 100% of patients received empiric antibiotic treatment. Similar data were observed in the series by Yang et al. and Barrasa et al. in which 94% and 88% of patients received antibiotics [20, 22]. Conversely, in the Tarragona study no case of coinfection was identified and only 11.6% of patients received antibiotics at ICU admission. Arentz et al. report an incidence of bacterial and viral coinfection of 4.8% and 14.3%, respectively. Bhatraju et al. did not find any cases of coinfection despite an active search [24]. It is possible that the differences observed are due to the definition used, including both cultures/serology results and elevation of biomarkers.

We were unable to detect any variable at MV onset that could help us predict worse clinical course either from the point of view of age or comorbidities, or from the viewpoint of inflammatory or respiratory parameters. Hua et al. observed that patients who required MV presented a lower lymphocytes count, and CRP levels were higher [26]. Wang et al. detected that also D-dimer was higher in patients requiring MV [30]. We have observed that patients from group B presented a higher O_2 A-a gradient and a lower pO_2/FiO_2 ratio after 7 days under MV. Persistence of moderate ARDS after 7 days of MV increases the risk of poor outcome (OR 6.417, CI 95% 1.091-37.735, p=0.040). This finding coincides with that published by Rodríguez et al. who reported that among patients who died, the pO_2/FiO_2 ratio did not improve after 7 days of treatment [19]

A notable aspect of our series is the low 28 days mortality rate (7.4%). Blake et al. presented ICU mortality of 21% (with 15 of the 39 patients still in the ICU) [21]. In the Italian and the Tarragona series, they also reported ICU mortality of 26% and 23.3% (28.1% among patients who received MV), respectively [19, 25]. Mortality was significantly higher in the remaining studies: 36% at 28 days in the Barrasa et al. series [22], 50% hospital mortality in the Bhatraju et al. [24] and Wang et al. series [30], 52.4% at 5 days in the Arentz et al. study [23], 61.5% at 28 days in the Yang et al. series [20] and up to 92% in patients with MV reported by Hua et al. [26]. This lower mortality does not appear to be related to less severity in our patients. As we have discussed, it is possible that the incidence of non-respiratory organ failure is lower for our patients, however, the respiratory failure is more severe and lasts longer. It could be considered that the reduced number of patients in our series did not entail an exceptional overload for our ICU, but 22 patients requiring MV simultaneously were treated, meaning an occupation of 157% of the beds usually available for MV. Once we know the results of RECOVERY trial, the use of corticosteroids may have been a reason for this low mortality (although 28 days mortality in mechanical ventilated patients receiving dexamethasone in this trial is 29.3%). We believe that some factors such as the experience managing ARDS patients of staff treating these patients, in addition to organization of the COVID-ICU, may have played an important role. However, we would not go so far as to attribute the reduction in our mortality to a specific single aspect.

Our study presents significant limitations. First, the reduced sample size, which hinders detecting possible discrepancies between groups. Second, the high survival observed prevents comparisons of groups based on mortality and led us to use a composite outcome (mortality or prolonged MV). Third, absence of a control group makes it impossible to draw definitive conclusions about methylprednisolone effect. Fourth, this is a single hospital series with some specific characteristics and some solutions applied in our hospital context, which complicates extrapolation of our results to another type of patient or center.

To conclude, our COVID-19 patients presented severe and long lasting ARDS; a short course of low dose corticosteroids appears to reduce the inflammation and temporarily improve the oxygenation. Only persistence of ARDS after 7 days under MV was a predictor of poor outcome.

ACKNOWLEDGEMENTS

Authors thank the Illustrious Medical College of Ourense for their collaboration in the English translation of this article

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/117.2020

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Seroprevalence and Trends of HTLV-1/2 among Blood Donors of Santo Domingo, Dominican Republic, 2012-2017

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Article history
Received: 6 October 2020; Revision Requested: 28 October 2020; Revision Received: 9 November 2020; Accepted: 13 November 2020; Published: 11 December 2020

ABSTRACT

Objectives. Being a Caribbean country, the Dominican Republic is considered endemic for HTLV-1. Viral screening in blood banks is recommended for this blood borne infection. The purpose of this work is to analyze the seroprevalence and trends of HTLV-1/2 in the Dominican Republic blood donors; it is focused on Santo Domingo, the capital of the country, which has the largest blood donation activity. We also aim at comparing our findings with published data from neighboring countries.

Patients and methods. We performed a retrospective cross-sectional study of 10 blood centers of Santo Domingo, which reported HTLV and the other blood-transmitted infections in full. They represent more than 40% of the province's blood donations. Annual seroprevalence of HTLV-1/2, period prevalence (2012-2017), and time trend were determined.

Results. A total of 352,960 blood donations were evaluated. The HTLV-1/2 period prevalence was 0.26% (929/352,960) (95% CI: 0.24–0.28%). We also found a marked predominance of replacement donation (90.4%) in comparison to voluntary contributions (9.6%). Therefore, this blood donor study may provide clues on the general prevalence of the infection.

Conclusions. Seroprevalence of HTLV-1/2 in blood donors of Santo Domingo, Dominican Republic, showed a relatively low and steady trend in the studied period.

Keywords: HTLV-1, Dominican Republic, blood donors, prevalence, Santo Domingo

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Seroprevalencia y tendencias de HTLV-1/2 en los donantes de sangre de Santo Domingo, República Dominicana, 2012-2017

RESUMEN

Objetivo. Como país caribeño, la República Dominicana es considerada endémica para HTLV-1. El propósito de este trabajo es analizar la seroprevalencia y la tendencia del HTLV-1/2 en donantes de Santo Domingo, que al ser la capital concentra la mayoría de las donaciones. También pretendemos comparar nuestros hallazgos con los datos de los países vecinos.

Pacientes y métodos. Hemos realizado un estudio transversal retrospectivo de los 10 centros de transfusión de Santo Domingo que comunicaron la detección de HTLV y las otras infecciones de transmisión sanguínea en su totalidad, que representan más del 40% de las donaciones de la provincia. Se determinó la seroprevalencia anual de HTLV-1/2, la prevalencia del período (2012-2017) y la tendencia temporal.

Resultados. Se evaluaron un total de 352.960 donaciones. La prevalencia de HTLV-1/2 en el período estudiado fue del 0,26% (929/352.960) (IC del 95%: 0,24–0,28%). Encontramos un marcado predominio de la donación de reemplazo en comparación con la voluntaria. Por lo tanto, este estudio puede proporcionar claves sobre la prevalencia general de la infección.

Conclusiones. La seroprevalencia de HTLV-1/2 en donantes de sangre de Santo Domingo, República Dominicana, ha sido relativamente baja y estable en el periodo estudiado.

Palabras clave: HTLV-1, República Dominicana, donantes de sangre, prevalencia, Santo Domingo

INTRODUCTION

Human Lymphotropic Virus (HTLV) is a complex deltaretrovirus that belongs to the Retroviridae family [1]. It has four known strains named HTLV-1, HTLV-2, HTLV-3 and HTLV-4. HTLV-1 is the most pathogenic one for humans, and it is primarily associated with Adult T cell Leukemia/Lymphoma (ATLL) and HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) [2]. HTLV-2 is rarely pathogenic, and it is only sporadically associated with neurological disorders [2].

HTLV-1 was first identified in 1979, when researchers from the Bethesda National Cancer Institute isolated the virus in a sample of Cutaneous T Lymphoma, later identified as ATLL. This was the first time that a link between a retrovirus and a human neoplasm was established [3].

HTLV-1 transmission routes may be vertical (mainly through breastfeeding), sexual or parenteral [4]. It is estimated that this virus affects at least 10 million people worldwide, producing pathologies in approximately 5% of the infected individuals. The main endemic regions for HTLV-1 are southwest Japan, Sub-Saharan Africa, Melanesia, South America, and the Caribbean [5].

Difficult access to the general population of specific areas and the non-homogeneous distribution of the virus makes it difficult to perform representative epidemiological studies. Therefore, information from selected populations, such as blood donors, is generally useful, since it grants access to large numbers of infected individuals, many of them asymptomatic. Furthermore, it allows us to break the chain of infection and to establish prevention strategies to avoid both the virus and its associated diseases.

Likelihood of HTLV-1 seroconversion after injection of contaminated blood products is approximately 40–60% [6]. Thus, the risk of transmission through asymptomatic blood donors should be considered, particularly in high prevalence areas. Therefore, it is crucial to validate the screening of donations for HTLV-1/2 with local epidemiological evidence [7].

The proportion of the different types of donors (voluntary/replacement) is different depending on the policies of each country. In some countries, donors are usually replacement donors, mainly family members or friends of hospitalized patients; sometimes, donors are illegally paid to give blood. Thus, epidemiological and demographic characteristics vary among blood donors. They can be entirely representative of the middle-class population in some countries, while in other areas, they may represent low socioeconomic populations [5]. In the Dominican Republic, where we have focused our study, blood donations are mainly made by replacement, with a wide socioeconomic and cultural diversity among these blood donors [8].

As a Caribbean country, the Dominican Republic has an estimated prevalence of HTLV-1 infection ranging from 1 to 5% [5]. Nonetheless, there are very few studies in this particular country, most of them focused on risk groups [9-11]. Therefore, new and specific studies are needed to estimate the infection more accurately.

The presence of HTLV-1/2 in blood donors of Santo Domingo was first detected in 1987, when Koenig et al. conducted a prevalence study in different populations of the Dominican Republic [9]. A total of 1955 healthy blood donors were evaluated at a National Laboratory, showing a 1.2% seroprevalence. These authors suggested that the country could have an overall incidence of 200-400 newly infected individuals each year. Still, the cost of blood screening and the fact that the majority (98-99%) of HTLV-infected individuals never developed symptoms made a screening program untenable [9].

More recently, Paulino-Ramirez et al. performed a study in which they collected and analyzed plasma from 200 participants co-infected with Human Immunodeficiency Virus (HIV); they were transactional sex workers and intravenous drug users of Santo Domingo and they presented an overall weighted seroprevalence of HTLV-1/2 IgG antibodies of 13.91% in men and 10.59% in women [11].

HTLV-1/2 has been screened in some blood banks of the Dominican Republic since 2005, but it was not until 2009 that it was fully implemented [8]. There are 63 blood banks in the country, half of which belong to the Ministry of Public Health. The private and military sectors manage the rest of the centers. In mid-2019, a National Hemocenter seeking to address the blood deficiency and raise the donation capacity of the Dominican Republic, was put into service [12].

It is particularly important to evaluate hemovigilance policies to ensure transfusion safety. The development of epidemiological studies is a valuable tool to achieve this purpose. This study aims at obtaining recent data on seroprevalence and trends of HTLV-1/2 in blood banks of Santo Domingo, Dominican Republic.

METHODS

Study design and population. We performed a retrospective cross-sectional study based on data obtained from the National Directory of Blood Banks (Public Health Ministry) of Santo Domingo, Dominican Republic. This included data collected from 10 transfusion centers of Santo Domingo (Dominican Red Cross, Salvador B. Gautier Hospital, Padre Billini Hospital, La Altagracia Maternity Hospital, Robert Read Cabral Child Hospital, Blood and Specialties Center, Dominican Medical Center, CEDIMAT, Referencia Clinical Laboratory, and Marcelino Velez Santana Hospital) during the 2012-2017 period.

Participants were blood donors that met the criteria established by the Ministry of Public Health in the Dominican Republic: aged between 18 and 65 years, or older than 16 years with parental consent; minimum weight of 110 pounds; no previous history of HIV, HBV, HVC, tuberculosis or organ transplant; no severe diseases or conditions such as cancer, heart failure or other severe chronic diseases; no current pregnancy or breastfeeding; no history of tattoos, piercings or acupuncture in the last 12 months; no consumption of alcoholic bever-

Table 1 HTLV I/II Seroprevalence of period 2012-2017 and type of donation (voluntary and replacement) in Santo Domingo

Year	HTLV I/II			Donation	
	Screened Samples	Positive samples	Seroprevalence	Voluntary (%)	Replacement (%)
2012	51,593	154	0.30%	7,634 (17%)	43,914 (86%)
2013	54,510	163	0.30%	6,157 (13%)	47,643 (87%)
2014	56,155	99	0.18%	4,993 (10%)	51,288 (90%)
2015	57,059	123	0.21%	5,348 (10%)	52,393 (90%)
2016	67,294	148	0.22%	4,332 (7%)	62,941 (93%)
2017	66,349	242	0.36%	5,537 (9%)	60,880 (91%)

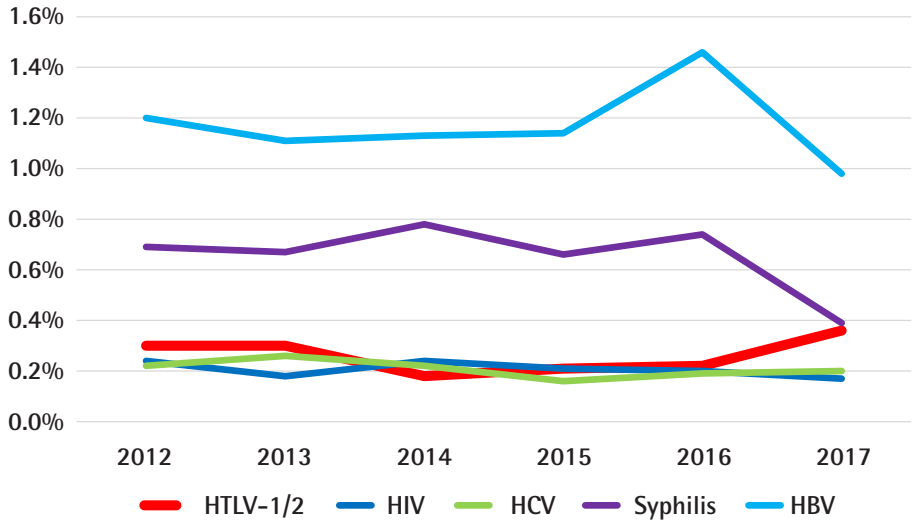

Figure 1 Seroprevalence and trends of HTLV-1/2 and other blood borne infections (HIV, HCV, HBV and syphilis) during 2012-2017 period in blood banks of Santo Domingo, Dominican Republic. Here, detection of HTLV-1/2 is shown in the context of other common blood transmitted microorganisms; so its relative impact and variation can be compared.

ages in the last 24 hours and not having undergone any major surgery in the last six months before donating blood [13].

The minimum sample size was estimated with a sample proportion of 50% following the formula used for qualitative variables of cross-sectional studies [14].

Detection tests. The serological tests were Enzyme-Linked Immunosorbent Assay (ELISA) and Chemiluminescence Immunoassay (CLIA).

Statistical analysis. Annual seroprevalence of HTLV-1/2 HIV, Hepatitis C Virus (HCV), Hepatitis B Virus (HBV) and syphilis, period prevalence (2012-2017), and time trend were determined. For this purpose, we used a time series analysis adjusted to a first-order moving average model. We also performed the least-squares method to estimate the secular trend. Statistical analyses were performed using R and Graphpad softwares.

Ethics. The present research was approved by UNIBE´s institutional review board and ethics committee (reference CEI-2019-03)

RESULTS

In Santo Domingo 25 blood banks use to report their data annually. Nonetheless, for the period 2012-2017, only 10 of them communicated their results fully. We selected these ten

Table 2 **Seroprevalence of HIV (Human Immunodeficiency Virus), HCV (Hepatitis C Virus), HBV (Hepatitis B Virus) and Syphilis in the period 2012-2017**

Year	Positive samples (seroprevalence)				Screened Samples
	HIV	HCV	HBV	Syphilis	
2012	125 (0.24%)	116 (0.22%)	621 (1.20%)	354 (0.69%)	51,593
2013	101 (0.18%)	140 (0.26%)	596 (1.11%)	368 (0.67%)	54,510
2014	135 (0.24%)	125 (0.22%)	720 (1.13%)	437 (0.78%)	56,155
2015	118 (0.21%)	92 (0.16%)	652 (1.14%)	379 (0.66%)	57,023
2016	136 (0.20%)	128 (0.19%)	985 (1.46%)	498 (0.74%)	67,294
2017	110 (0.17%)	129 (0.20%)	649 (0.98%)	260 (0.39%)	65,685

centers to analyze the HTLV-1/2, HIV, HCV, HBV and syphilis prevalence and trend for this period, thus avoiding incomplete information that could introduce a bias in our study. All of them are located in Santo Domingo city and represent more than 40% of the province's blood donations.

A total of 352,960 blood donations were evaluated by ELISA or CLIA (Table 1 and Figure 1).

HTLV-1/2 period prevalence was 0.26% (929/352,960) (95% CI: 0.24–0.28%). Overall HTLV-1/2 prevalence was 263 per 100,000 donations during the six years.

Annual HTLV-1/2 prevalence was 0.30% in 2012, 0.30% in 2013, 0.18% in 2014, 0.21% in 2015, 0.22% in 2016 and 0.36% in 2017, indicating that there was no significant secular trend during the 2012–2017 period (p for trend=0.5596).

Seroprevalence and trends of HIV, HCV, HBV and syphilis in the period 2012-2017 are shown in Figure 1 and Table 2.

The type of donation (voluntary and replacement) was studied. As detailed in Table 1, voluntary donations represented 9.6% (34,001/353,060) and replacement donation 90.4% (319,059/353,060).

DISCUSSION

We have analyzed seroprevalence and trends of HTLV-1/2 in blood banks of the capital city of the Dominican Republic, Santo Domingo. Most studies on HTLV-1 have been performed in Japan; other areas, like the Caribbean countries, are globally considered without understanding the substantial differences between them. Being a Caribbean country, the Dominican Republic is deemed endemic for HTLV-1. Nonetheless, there are very few epidemiological data about this virus, even though HTLV-1/2 has been fully screened in Dominican blood banks since 2009.

For the present study, we selected ten blood banks of Santo Domingo city, which collected most of the city's blood donations and studied them for the period 2012-2017. We show here a period prevalence of 0.26% of HTLV-1/2 among blood donors. The trend of HTLV seroprevalence in the studied period (2012-2017) seems to be low and steady, like the other blood-borne diseases reported in the same period. Also, it showed similar data to those reported by the Ministry of Public Health for blood donors of the Dominican Republic in the period 2005-2011 [8]. However, by the time the first HTLV study on Dominican blood donors took place in 1987 seroprevalence was 1.2%. Since the implementation of a HTLV-1/2 blood unit screening in 2005, a lower prevalence has been shown, probably due to recent improvements in donor selection and blood donation policies [8].

Latin America and the Caribbean cannot be considered as a homogeneous region. Each country has different blood donation models (voluntary, replacement, non-remunerated, remunerated) and ethnic background. Several studies performed on large populations of blood donors have found differences in seroprevalence depending on the geographical location and ethnic origin of the donors [5, 15]. Most inhabitants of the Caribbean region are of African ancestry; in fact, HTLV-1 prevalence has been found to be higher in areas populated with inhabitants of African descent in comparison with those inhabited by people of mixed and white descent. This is the case of Brazil, where the prevalence of HTLV-1/2 in blood donors is heterogeneous, ranging from 0.04 to 1% [5, 16-22] and a large study on Brazilian blood donors showed that regional differences in HTLV-1 prevalence are probably due to the ethnic origin of the underlying population. A higher prevalence in colored donors (2.14/1,000), versus mixed-race donors (1.58/1,000), or white donors (0.79/1,000) was shown [5, 15]. In Peru, very few studies on HTLV-1 have been done in blood donors, showing a prevalence of around 0.9% [23]. Colombia shows a seroprevalence of HTLV-1/2 in the population of blood donors in Cali and Medellín of 0.24% and 0.176%-0.06%, respectively [24-26]. Also, a retrospective study analyzing screening and positivity for HTLV-1 and 2 data collected from 2001 to 2014 by Colombian blood banks, showed a cumulative reactivity of 0.30% [27]. Chile and Argentina, with a population of predominantly European origin, seem to have a low and exceptionally low seroprevalence of HTLV-1 of 0.10% and 0.011% respectively [28, 29]. Paraguay shows a prevalence of 0.37% according to the available information[30].

There is not much information available on Central America, but some studies indicate a seroprevalence of HTLV up to 0.14% in Honduras and 0.22% in Costa Rica [31, 32].

Other studies on blood donors of the Caribbean region also suggest a higher prevalence in countries where people are of predominantly Black descent, such as Jamaica, where studies show a prevalence of 2.5% (376/15,022) and 3.8% (30/794) [33, 34]. These dynamics are less evident in Haiti, where according to the 2015 report of the Panamerican Health Association there were 0.78% (216/27,752) positive blood units; and in the French West Indies (Martinique and Guadeloupe), where HTLV-1 seroprevalence in blood donors is around 0.4–0.3% [35, 36]. On the contrary, in countries like Cuba, where there are relatively few African ancestry persons compared with the previously mentioned countries, there is a very low prevalence of HTLV in blood donors of 0.01% (3/16,920) [37]. Consistently, Puerto Rico seems to have a low HTLV prevalence: around 0.25% (1/400) [38]. This rate is similar to the one we found in Santo Domingo, as could be expected due to their common historical and ethnographic background and the likenesses in their populations, where mixed-race is predominant. Nonetheless, further studies are needed to confirm the absence of HTLV foci in certain areas that might lead to an increase in global prevalence among blood donors.

Despite, globally speaking, HTLV-1/2 seroprevalence in the Dominican Republic's blood donors seems to be low, the situation of the border provinces is not fully known, especially in remote areas where there are not even blood banks, not to speak of HTLV studies. Thus, additional studies focused on these provinces are needed; there, Haitian immigration is higher, something which could confirm the increase of viral transmission among this type of population.

Our findings of this study cannot be extrapolated to the general population, as blood donors are usually not representative –they are selected according to the blood safety protocols of each center and to country policies and so doing this could lead to bias and to an underestimation of HTLV prevalence. Thus, real HTLV prevalence among the general population of Santo Domingo and in the rest of the country could be higher than the one observed, especially if we consider that we limited the data analysis to the ten blood centers of Santo Domingo which fully reported their information on HTLV and the other blood-borne infections in the period studied.

Although these results may not be fully representative of the general population nor of the donor population of the entire country, they could well be a guidance of HTLV-1/2 seroprevalence and trend in blood donors of Santo Domingo and give a hint on the prevalence in the wider population. Blood donors use to belong to primarily low-risk populations. However, the predominance of replacement donation and the diversity of origins of the capital inhabitants allows this study to be more representative of the city population and supports the idea of a lower prevalence of HTLV-1 in the Hispanic Caribbean countries in comparison with other areas with a higher proportion of African ancestry population. However, studies on larger and broader populations are needed in order to confirm this hypothesis.

In the Dominican Republic, confirmatory testing of reactive donations is not performed in all blood centers. Ours is a study based on real-world diagnostic data with both the advantages and limitations of a work of this kind. The main drawback is the lack of confirmation of the results with other techniques in most of the centers and the absence of records of HTLV-1 and HTLV-2 discrimination in those performing western blot (WB) as confirmatory test. However, this also shows the need to improve blood bank procedures in Dominican Republic and probably in most of the HTLV endemic countries.

Tests commonly used for HTLV-1/2 confirmation and to differentiate between HTLV-1 and HTLV-2 infection are WB or innogenetics line immunoassay (INNO-LIA) and qualitative and/or quantitative polymerase chain reaction (PCR). Despite some improvements in the specificity of WB assays, indeterminate serological patterns are frequent and represent an important concern for routine screening and a major issue for comparative analyses between epidemiological studies [5, 39]. INNO LIA, although is not so commonly used as WB, represents a good alternative, especially in co-infected patients, in which indeterminate result of WB could be an issue [40]. PCR is useful for the diagnosis and follow-up of HTLV-1 associated diseases such as ATLL and TSP/HAM. Moreover, it provides amplicons for sequencing analysis to determine the HTLV-1 genotype and generate molecular epidemiological data to better comprehend the evolutionary past of this virus [41]. However, this is a more expensive and complex test, thus it is not available in most blood centers of developing countries. We aim at validating and implementing this method for future studies in the Dominican Republic.

Notwithstanding the previous statements, it is essential to continue improving donor selection because a higher prevalence could be found in high-risk populations. Also, it is necessary to encourage voluntary blood donation, which nowadays represents only approximately a 20% of all blood donations in the Dominican Republic. This could improve blood safety and guarantee the blood supply of the country.

FUNDING

None to declare

ACKNOWLEDGEMENTS

We would like to thank the Blood Bank National Directory from the Dominican Public Health Ministry for providing us with the epidemiological data for this work and Fundación Hay Esperanza for support.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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Official journal of the Spanish Society of Chemotherapy

Brief report

Revista Española de Quimioterapia
doi:10.37201/req/085.2020

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Clostridioides difficile infection in a long-term convalescence hospital: A real tale of pitfalls and outdated therapy

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Article history
Received: 29 July 2020; Revision Requested: 22 September 2020; Revision Received: 30 September 2020; Accepted: 6 October 2020; Published: 1 December 2020

ABSTRACT

Objective. The aim of the study was to know the characteristics and risk factors of *Clostridioides difficile* infection (CDI) in a long-term hospital is key to improve its management.

Material and methods. Retrospective study with 37 patients, along 43 months. We describe demographic variables, clinical data, time to diagnosis, treatment, and evolution.

Results. Analysis of 46 episodes (37 patients, mean age=82.2 years). 77.8% were absolutely dependent, 41.7% had chronic kidney disease, 64.9% had received antibiotics in the previous three months, 40.5% received antibiotics at diagnosis. It was the first episode in 78.4%, and first recurrence in 21.6%. Therapy was started in the first 24 hours after diagnosis in 89.2%, mostly metronidazole. 83.3% recovered, 3 patients died from CDI, diagnosis was registered in the discharge report in 91.1%.

Conclusions. Previous antibiotic therapy, high grade of dependency and renal failure were the main risk factors. There is room for improvement in CDI management at our hospital.

Keywords *Clostridium difficile*, *Clostridioides difficile*, nosocomial infection, recurrent infection, management.

Infección por *Clostridioides difficile* en un hospital de convalecencia: una historia real de trampas y tratamiento anticuado

RESUMEN

Objetivo. Conocer las características y factores de riesgo de infección por *Clostridioides difficile* (ICD) en un hospital de convalecencia es clave para mejorar su manejo.

Material y métodos. Estudio retrospectivo con 37 pacientes, durante 43 meses. Describimos variables demográficas, datos clínicos, tiempo hasta el diagnóstico, el tratamiento y la evolución.

Resultados. Análisis de 46 episodios (37 pacientes, edad media=82,2 años). 77,8% tenían dependencia absoluta, 41,7% enfermedad renal crónica, 64,9% habían recibido antibióticos en los 3 meses previos, 40,5% recibían antibióticos en el momento del diagnóstico. Fue el primer episodio en 78,4%, y la primera recidiva en 21,6%. En el 89,2% se comenzó tratamiento en las primeras 24 horas tras el diagnóstico, mayoritariamente metronidazol. El 83,3% se recuperaron. 3 pacientes murieron por ICD. El diagnóstico figuraba en el informe de alta en 91,1%.

Conclusiones. El tratamiento antibiótico previo, un alto grado de dependencia, y el fracaso renal, fueron los factores de riesgo principales. Hay margen de mejora en el manejo de ICD en nuestro hospital.

Palabras clave: *Clostridium difficile*, *Clostridioides difficile*, infección nosocomial, infección recurrente, manejo

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INTRODUCTION

Clostridioides difficile infection (CDI) is the most frequent cause of nosocomial diarrhoea. It is a global health problem, with most cases acquired in hospital but also described in the community. Reported mortality rate ranges between 3-15%, and recurrence rate, 12-40% [1,2].

Hospital San Juan de Dios (HSJD) is a long term-acute care hospital with 188 beds, holding units of palliative care, neurorehabilitation, haemodyalisis for chronic patients, convalescence, and an acute geriatric unit. Patients are admitted from acute care hospitals of the region, and directly from nearby centres of primary care, with a catchment area of 500.000 inhabitants. These types of health facilities have their own features and challenges concerning CDI [3,4].

MATERIAL AND METHODS

We have performed a retrospective study of all CDI cases since 5th May 2016 to 31st December 2019. We used the definitions of nosocomial, community-acquired and recurrent CDI reported in updated guidelines [5,6]. In every patient with a clinical picture suggestive of CDI (diarrhoea, abdominal pain, fever), a faecal sample was collected and analysed at the microbiology laboratory of the hospital, using *C. difficile quik check complete* (Techlab® Blacksburg) test. This is a fast membrane enzyme-immunoassay which simultaneously detects the bacterial antigen glutamate dehydrogenase (GDH) and also toxins A and B. Samples which were GDH+/Tox- were sent to the reference hospital (Hospital Miguel Servet) for Polymerase Chain Reaction –PCR- testing (GenXpert®Cepheid), which detects a toxin-producer gen [7]. Data obtained from clinical records were fully anonymised and collected using a specifically designed database. For the statistical study, qualitative variables are presented according to distribution of frequencies, and expressed as number and percentage. Quantitative variables are presented as means, median, mode and standard deviation. We did all statistical analysis using SPSS (IBM SPSS Statistics 25.0 2017). The Ethics Committee of Clinical Research of Aragón (CEICA) approved the study project (ruling 31/01/2020), as did the Ethics Committee of HSJD.

RESULTS

Patients, risk factors and clinical data. We describe 37 patients diagnosed of CDI during the study period (24 men/13 female), mean age 82.8 +/- 9.6 years (56-100). Patient´s demographics and clinical data before and on admission appear in Table 1.

CDI diagnosis, treatment and clinical outcome. (Table 2) There were 46 episodes of CDI (29 first episodes and 17 recurrences). In 29 patients (78.4%) the infection was the 1st episode, and in 8 cases (21.6%), the debut episode in our hospital was the first recurrence of CDI. 12 patients out of the 37 presented recurrent CDI during their hospital stay: 8, first recurrence after an initial episode (21.6%), 8 as second recurrence, and 1 as third recurrence (overall, 17 episodes in 12 patients). Data concerning the characteristics of the infection (clinical data, treatment, evolution) appear in Table 2.

In 15 patients with CKD and age > 65 years, CDI was qualified as severe, with a high risk of recurrence according to the guidelines.

The anti-CDI therapy of the first episode was metronidazole in 24/29 (82.8%), vancomycin in 4/29 (13.8%), and fidaxomicin in one. The first CDI recurrence was treated with metronidazole in 5 cases, and with vancomycin in 3 cases. The second CDI recurrence was treated with metronidazole in 1 case, vancomycin 2 cases, fidaxomicin 1 case. The third recurrence received fidaxomicin.

DISCUSSION

We describe in this study the characteristics of 37 patients with CDI in a long term-acute care hospital, trying to confirm if the well-known reported risk factors are also present in our patients, and if the diagnostic and therapeutic approaches employed fit with current guidelines. Most studies have been performed in health facilities of very different profile (tertiary hospitals [8,9], multicentric studies [10], or extensive epidemiological studies [2]). After a thorough bibliographical search, we have not found any study performed in a hospital of our profile.

In our series, almost 60% of patients came from emergency departments of other hospitals, for convalescence and/or rehabilitation after infections or cerebrovascular disease. As symptoms may be scarce or not reported, and given the high index of dependency in this population, diagnosis may be a difficult challenge. It is also worth mentioning, as it has been reported in other series [10], the association between CDI and chronic renal insufficiency (15 from 36 patients, 41.7%, had an eGFR<50mL/min). All these factors confer to our patients a high degree of frailty and a high risk of CDI recurrence, a finding also previously described [8,11,12]. We also found in our patients a wide use of PPIs, drugs that modify the pH of the bowel and disrupt bowel microbiota, as well as an association of CDI with previous antibiotic use, also described in previous studies [3,4,8-11]. It is important to remark that 40.5% of patients were on antibiotics at the time of diagnosis, and they were withdrawn in only 53.5% of them, which may indicate a pitfall in the management of CDI in our patients.

Concerning clinical presentation, most (83.8%) patients did not refer any symptoms or signs. This scarcity of clinical data indicates that CDI is clinically silent in this population, even in severe cases. Though there are no registered data regarding the number of leukocytes, applying the GEIH Score [12] (age, number of diarrhoeal episodes and renal insufficiency), 40.5% of patients had severe CDI, with a high risk of recurrence.

Regarding the analysis of the episodes, in 78.4% of cases CDI presented as the first episode. In 21.6% of cases, the epi-

Table 1 **Patients´ demographics, clinical data before and on admission.**

Variable	Number (n)	Percentage (%)
Patients´ demographics		
Gender		
Female	24/37	64.9%
Male	13/37	35.1%
Age	Mean ± SD = 82.8 ± 9.6	
Origin		
Emergency department	22/37	59.5%
Neurology	4/37	10.8%
Pre-diagnosis data		
Patients with infections in the previous 3 months	24/37	64.9%
Number of infections	N=28	
Respiratory infection	8/28	28.6%
CDI	8/28	28.6%
Urinary tract infection	6/28	21.4%
Patients with antibiotics in the previous 3 months	24/37	64.9%
Number of antibiotics	N=38	
Beta-lactams	20/38	52.6%
Glucopeptides	5/38	13.2%
Macrolides	5/38	13.2%
Clinical data on admission		
Diagnosis on admission		
Respiratory infection	7/37	18.9%
Unspecified diarrhoea	6/37	16.2%
Sepsis	5/37	13.5%
Stroke	4/37	10.8%
Days of disease that led to admission	Mean ± SD =17.8 ± 21.2	
Patients with antibiotics on admission	21/37	56.8%
Number of antibiotics	N=23	
Beta-lactams	16/23	69.6%
Quinolones	2/23	8.7%
Barthel on admission	Mean ± SD =15.8 ± 24.4*	
CKD	15/36*	41.7%*
PPIs	29/37	78.4%

CKD=chronic kidney disease, (estimated Glomerular Filtration Rate<50mL/min); PPIs=proton pump inhibitors.
***Data about clinical outcome was missing in one patient.**

sode during hospital stay was a recurrence, as the initial episode had happened previously. According to the current definition of recurrence given by IDSA-SHEA [6], it can be said that 32.4% suffered from recurrent CDI, and 67.5% (n=25), only an initial episode of CDI, without further recurrences during the length of the hospital stay. This recurrence rate is between 20 and 30% in the study by Lessa et al. [2] and similar in other studies [8,11]; it is reported as high as 57.1% in one of the studies performed in Spain [11].

In most cases, treatment was started within the same day or the following day after reception of the laboratory diagnosis, which can be a good quality indicator. Considering

Table 2 **Clinical data of CDI, treatment and evolution until discharge.**

Variable	Number (n)	Percentage (%)
Clinical data of CDI		
Distribution patients-year		
2016	2/37	5.4%
2017	9/37	24.3%
2018	10/37	27%
2019	16/37	43.2%
CDI origin		
Nosocomial	32/37	86.5%
Community	5/37	13.5%
Patients with antibiotics on diagnosis	15/37	40.5%
Number of antibiotics	N=19	
Beta-lactams	11/19	57.9%
Cotrimoxazole	3/19	15.8%
Withdrawal of antibiotics on diagnosis	8/15	53.3%
Clinical findings		
Haemodynamic instability	0	0%
Tachycardia	1/37	2.7%
Nausea/vomiting	3/37	8.1%
Abdominal pain	6/37	16.2%
Fever	10/37	27%
Diarrhoea	35/37	94.6%
>2 days	20/37	54.1%
Initial episode during hospital stay		
First episode of CDI	29/37	78.4%
First recurrence	8/37	21.6%
Recurrent CDI	12/37	32.4%
Treatment		
Started ≤ 1 day after diagnosis	33/37	89.2%
Antimicrobials		
First episode		
Metronidazole	24/29	82.8%
First recurrence		
Metronidazole	8/12	66.6%
Contact precautions	26/37	70.3%
Evolution until discharge		
Recovery	31/36*	86.1%*
Derivation to other center	1/37	2.7%
Death attributable to CDI	3/37	8.11%
Days of hospital stay	Mean ± SD = 43.6 ± 30.0	
Days diagnosis-discharge	Mean ± SD = 23.0 ±19.2	
Microbiological control	4/37	10.8%
CDI as principal diagnosis in discharge report	7/37	18.9%
CDI specified in discharge report	34/37	91.9%

CDI = *Clostridiodes difficile* infection; * Data about clinical outcome was missing in one patient.

therapeutic approach, 78.4% of individuals with an initial episode were treated with metronidazole, which was the drug of choice until 2017. However, last guidelines [5,6] advise about the use of vancomycin or fidaxomicin as first line in all patients with first episode of CDI [13-15]. So, it could be said that the degree of penetrance of current therapeutic guidelines is poor in our hospital. Recurrent episodes were also treated inadequately, mostly with metronidazole again.

Despite this, 83.8% of the patients recovered, a similar high rate is reported by Aljafel et al. [9] and others [8] 8.1% of deaths in our series were attributable to CDI. This figure is similar to the rate reported by Olsen et al. [15] and also by Lessa et al. [2] and it is even higher in other series [1,8,10]. It is worthwhile to remember that all publications belong to health facilities with very different characteristics from our hospital. Mean hospital stay of our patients was 43.6 days (standard deviation: 30.1 days), which is longer than the duration reported by other authors [8,9]

We acknowledge the limitations of the study: retrospective, with a small sample, and patients who are far from representative of the general population, as are aged (mean age 82 years) and with multiple comorbidities. It means that CDI is bound to be more severe and the risk of recurrences, higher. However, it has also strengths: it can inspire further research about CDI in the hospital, within the frame of a stewardship team and infection control approach. Moreover, it analyses a type of patients which is specific to this profile of hospitals, scarcely represented in current literature.

FUNDING

None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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Official journal of the Spanish Society of Chemotherapy

Brief report

Revista Española de Quimioterapia
doi:10.37201/req/090.2020

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Dual therapy with raltegravir plus a fixed dose combination of darunavir/ritonavir in people living with HIV in Argentina

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Article history
Received: 7 August 2020; Revision Requested: 16 September 2020; Revision Received: 21 September 2020; Accepted: 29 september 2020; Published: 3 December 2020

ABSTRACT

Objective. There are generic fixed-dose combinations (FDCs) of ritonavir-boosted darunavir (DRV/r) available in Argentina. Experiences with these FDCs in dual therapy remain limited in clinical practice. We aimed to describe clinical and virologic outcomes in patients exposed to FDC DRV/r + raltegravir (RAL) 400 mg every 12 h in a real-life setting.

Patients and methods. Retrospective analysis of electronic medical records of HIV-infected patients under FDC DRV/r + RAL in an HIV clinic in Argentina (2014-2018). Individuals were classified as "switch group" (SG, undetectable viral load [VL] with any toxicity/comorbidity) and "virologic group· (VG, detectable viremia and infection by multidrug-resistant HIV).

Results. Of 7,380 patients on ART, 116 (1.5%) received FDC DRV/r + RAL, being 58% in SG. Sixty percent received DRV/r 800/100 mg dose (rest, 600/100 mg). The median (IQR) age and CD4+ T-cell count were: 52 (42-58) years, and 373 cell/µL (202-642). Ninety-eight percent were ART-experienced with a median of 3 (IQR 2-5) prior treatments. Main reasons for switch (SG) were renal (57%), cardiovascular (54%) and bone (14%) comorbidities. Median exposure to DRV/r + RAL was 18 months. Among patients in SG, 98% and 96% had undetectable VL at 6 and 12 months; in the VG, 89% and 87% had undetectable VL at 6 and 12 months. No patient required suspension due to toxicity/ intolerance.

Conclusion. In this cohort of mostly experienced HIV-infected patients, FDC DRV/r + RAL was effective and safe. Such therapy may be considered an option for patients with comorbid conditions and/or with multidrug-resistant HIV.

Keywords: HIV infection, antiretroviral therapy, dual therapy

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Terapia dual con raltegravir mas una combinación a dosis fija de darunavir/ritonavir en personas viviendo con VIH en Argentina

RESUMEN

Objetivo. Existen combinaciones genéricas de dosis fija (FDC) de darunavir/ritonavir (DRV/r) en Argentina. Las experiencias con estas FDCs en terapia dual siguen siendo limitadas. Nuestro objetivo fue describir los resultados clínicos y virológicos en pacientes expuestos a FDC DRV/r + raltegravir (RAL) 400 mg cada12 h en la práctica clínica.

Pacientes y métodos: Análisis retrospectivo de historias clínicas electrónicas de pacientes infectados por VIH con FDC DRV/r + RAL en Argentina (2014-2018). Los individuos fueron clasificados como: "grupo de cambio" (GC, carga viral [CV] indetectable con toxicidad/comorbilidad) y "grupo virológico" (GV, viremia detectable e infección por VIH multirresistente).

Resultados. De 7.380 pacientes en tratamiento antirretroviral (TAR), 116 (1.5%) recibieron FDC DRV/r + RAL, siendo 58% GC. El 60% recibió DRV/r 800/100 mg (resto, 600/100 mg). La mediana (IQR) de edad y de linfocitos T-CD4+ fueron: 52 (42-58) años y 373 células/µL (202-642). El 98% tenía experiencia en TAR con una mediana de 3 (IQR 2-5) tratamientos previos. Las razones para el cambio (GC) fueron las comorbilidades renales (57%), cardiovasculares (54%) y óseas (14%). La mediana de exposición fue 18 meses. En GC, 98% y 96% tuvieron CV indetectable a 6 y 12 meses; en GV, 89% y 87% a 6 y 12 meses. Ningún paciente requirió suspensión debido a toxicidad o intolerancia.

Conclusión. En esta cohorte de pacientes experimentados en TAR, la FDC DRV/r + RAL fue eficaz y segura. Dicha terapia puede considerarse una opción para pacientes con comorbilidades y/o VIH multirresistente.

Palabras clave: Infección por VIH, terapia antiretroviral, terapia dual

INTRODUCTION

Until recently, HIV treatment guidelines recommended triple antiretroviral therapy (ART) based on combining a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone with a third agent, such as a ritonavir-boosted protease inhibitor (bPI), an integrase inhibitor (INSTI) or a a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1-3]. However, toxicities associated with long-term use of NRTIs have led to the assessment of dual therapy approaches that do not include this drug class [4]. Cohort studies describe an increased prevalence of comorbidities associated with natural aging, including renal, cardiovascular, metabolic disorders such as diabetes, dyslipidaemia and osteoporosis, among others [5-7]. These comorbid conditions appear in people living with HIV at younger ages than non-infected controls [6-8]. Drug-related adverse events associated with the long-term use of NRTIs, as other antiretrovirals, may contribute to these comorbidities [9].

Some studies have suggested a possible improvement of NRTI-related adverse events after switching to NRTI-sparing regimens. These regimens could potentially achieve and maintain viral suppression and immunologic control, reduce costs, while avoiding long term toxicities. It can also be an alternative for patients under failing regimens (eg. patients with resistance to NRTI and other drug classes) [1-4].

In Argentina, DRV/r 800/100 and 600/100 mg generic fixed-dose combinations (FDC) are available and recommended (with a NRTI backbone) for naive or experienced patients in local guidelines [3,10]. The FDC considerably reduces the pill burden of this bPI, allowing better tolerability. Despite this FDC showed efficacy and low prevalence of adverse events in a randomized control trial in naïve patients [11], there are no publications considering its effectiveness and safety in routine clinical practice.

Raltegravir (RAL) was the first available INSTI, approved for use in Argentina in 2008 and, until recently, the most widely used drug of this family. It leads to potent viral suppression while maintaining a favorable adverse effect profile and minimal drug interactions. Its effectiveness to rapidly control HIV viral load (VL) has been demonstrated in antiretroviral-naive and experienced patients. However, its low genetic barrier precludes its use in patients with drug resistance mutations unless associated with accompanying drugs with higher genetic barrier, such as bPIs [12-14].

Experience with DRV/r + RAL dual therapy has been limited in clinical practice with no publications considering the use of a generic FDC of DRV/r. Addressing this information will contribute to guide use of ART in certain HIV-infected populations, we aimed to describe indications, efficacy and safety of a generic FDC of DRV/r + RAL 400 mg BID in real-life patients.

PATIENTS AND METHODS

We performed an observational retrospective cohort study carried out in a reference private center dedicated to the care of people living with HIV based in in Buenos Aires city, Argentina, with a network all over the country. The DT regimen was chosen on routine clinical practice basis by an infectious disease's specialist considering prior ART exposure, cumulative resistance profile, comorbidities, co-medications, history of adherence and tolerability to antiretrovirals, VL and CD4-T cell count.

The inclusion criteria were the following: HIV-infected patients older than 18 years, assisted in our institution network between January 2014 and December 2018, who have received DT with DRV/r + RAL for at least 24 weeks. Patients with evidence of resistance to DRV or RAL, active hepatitis B or pregnancy, or insufficient clinical and/or analytical information were excluded.

The information was obtained from the electronic medical records (Infhos® database). Data were retrospectively collected from the introduction of the DT until the last follow-up routine visit available within the study timeframe. Data collection included demographic and clinical variables (prior ART, clinical reason for indication, adverse events, virological and immunological response at 24 and 48 weeks after DT prescription). Individuals were classified as:

- *Switch group (SG):* suppressed patients (undetectable viral load) who switched due to toxicity or comorbidities and
- *Virologic group (VG):* HIV-infected patients with detectable viremia and infection by multidrug-resistant HIV (resistance to at least 2 drug classes)

Statistical analysis. For data analysis, categorical variables were described using absolute and relative frequencies and compared by $\chi 2$ test or Fisher's exact test according to expected values. Continuous variables were described using medians and interquartile ranges (IQR) and compared by t-test or Mann-Whitney test according to normality of variables. A two-sided p-value of <0.05 was considered significant.

RESULTS

Of 7,380 HIV-infected patients on ART in our institution, 236 (3.19%) received DT and 116 received FDC DRV/ + RAL. This DT regimen was the most frequently prescribed and accounted for 1.57% of our total population. Considering demographics, 69.8% were male and the median of age was 52 years (IQR 42-59). The majority of patients were experienced in ART (98%) with a median time of exposure of 144 months (IQR 75-228). Considering group classification, 68 (58%) individuals corresponded to SG and 48 (42%) to VG.

Clinical and immunovirological profile and time on dual therapy are shown in table 1. Patients in SG were older ($t = 5.1029$; $p<0.001$), had higher CD4 T-cell count prior to DT ($t = 4.7071$; $p<0.001$), and had been exposed longer ($t = 7.8199$; $p<0.001$) to more ART regimens ($z = 8.791$; $p<0.001$) than those in the VG. Both groups had a median of 2 prior virologic failures, with patients in VG with additional ongoing failure at DT indication. Regarding prior ART: 88.8% of the patients were re-

Table 1 **Demographic and immunovirological profile of 116 HIV-infected patients under dual therapy (DT) with a generic fixed dose combination of DRV/r + RAL in Argentina (2014-2018). Values are number (percentages) unless otherwise stated. Switch and virologic groups are compared.**

Variable	Overall N=116	Switch group n=68	Virologic group n=48	p-value
Age in years, median (IQR)	52 (42-58)	54.5 (49-60)	43 (32.5-52.5)	<0.001
Gender				
Female	35 (30.2%)	18 (26%)	17 (35%)	0.30
Male	81 (69.8%)	50 (74%)	31 (65%)	
CDC category				
A	19 (16.4%)	12 (18%)	7 (15%)	0.30
B	44 (37.9%)	29 (43%)	15 (31%)	
C	53 (45.7%)	27 (40%)	26 (54%)	
Months in ART pre-DT, median (IQR)	144 (75-228)	180 (108-240)	120 (36-180)	<0.001
Number of ART regimens, median (IQR)	3 (2-5)	4 (3-6)	2.5 (1-4)	<0.001
Months with viral load ≤50 copies/mL before DT, median (IQR)	11 (0-60)	48 (23-108)	0	<0.001
Number of previous virologic failures, median (IQR)	2 (1-3)	2 (1-3)	2(1-3)	0.047
Cd4+ (cell/uL) count before DT, median (IQR)	343 (196-646)	454 (338-772)	210 (106-407)	<0.001
Viral load (copies/mL) pre DT				
<50	64 (55.2%)	64 (94%)	0 (0%)	<0.001
50-200	4 (3.4%)	2 (3%)	2 (4%)	
>200	48 (41.4%)	2 (3%)	46 (96%)	
Time in DT, months, median (IQR)	17 (10-25)	18.5 (9-25.5)	15.5 (10-24)	0.718

ceiving triple therapy, being the most frequent the association of 2 INTI + bPi or NNRTI (detail shown in table 2).

Main reasons for prescription of DT in SG were renal (57%), cardiovascular (54%) and bone (14%) comorbidities, while in the VG the indication was exclusively as rescue therapy in the context of infection by multidrug resistant HIV. Regarding dosage used, 69 (59%) and 18 (37,5%) received FDC DRV/r 800/100 mg QD in the SG and VG, respectively (rest, 600/100 mg BID).

High prevalence of virologic suppression was observed at 24 and 48 weeks in both groups (table 3), with a trend to higher rates in SG. In 6 cases (4 from de VG and 2 from the SG) with VL >200 c/ml at 48 weeks, a resistance test was performed, showing emerging resistance to RAL (N155 pathway) in one patient from the VG. No patient developed resistance to DRV/r. No discontinuations of DT due to adverse events (toxicity or intolerance) were observed. Considering mortality, one individual (1.47%) in the SG group died of non-HIV related cause (septic shock in a diabetic patient with chronic renal disease).

DISCUSSION

Effective ART is the most important intervention in terms of improving quality of life and survival in HIV-infected population. This therapy should involve combinations of drugs recommended by current guidelines, mostly based on two NRTIS plus a third drug, which may vary according to regional policies: INSTI, NNRTI, or a bPI [1-3]. Despite current drugs are safe and with minimal tolerance issues, certain proportion of patients may require an individualized approach due to either comorbidities or resistance that precludes the use of NRTIs and other drug classes [4,9,15].

As far as we know, in this study we provide the largest experience in DT based in the use of DRV/r + RAL in a real-life setting using exclusively a generic FDC of the bPI. Our population represents ART-experienced patients in two complex clinical scenarios: those with comorbidities that required a NRTI-sparing regimen to prevent/minimize mainly renal and cardiovascular adverse events, and patients with limited therapeutic options due to multidrug-resistant HIV. Despite other INSTIs (elvitegravir, dolutegravir) were approved for use in Argentina during the period of the study, access was limited until recently and no experience in dual therapy in clinical practice could be documented. Of, note elvitegravir (with cobicistat booster) is only available as triple drug combination and not as independent medication. Bictegravir was approved in 2019 in Argentina and is available only as part of a coformulation with tenofovir alanfenamide and emtricitabine.

Table 2 Prior ART exposure (last regimen) in patients with prescription of a fixed dose combination of DRV/r + RAL in Argentina

ARV family prior to DT	% subjects N = 116
2 NRTIs	1 (1.0%)
3 NRTIs	1 (1.0%)
3 NRTIs + NNRTI	1 (1.0%)
4 NRTIs + NNRTI	1 (1.0%)
2 NRTIs + ANTCCR5	1 (1.0%)
NRTI +ANTCCR5 + bPI + INSTI	1 (1.0%)
2 NRTIs + bPI + ANTICCR5	1 (1.0%)
NNRTI + bPI + INSTI	1 (1.0%)
NRTI + NNRTI + bPI	1 (1.0%)
2 NRTIs + INSTI	2 (1.9%)
NNRTI + bPI	2 (1.9%)
NRTI + bPI + INSTI	2 (1.9%)
2 NRTIs + NNRTI + bPI	3 (2.9%)
ANTCCR5 + bPI	3 (2.9%)
3 NRTIs + bPI	9 (8.7%)
bPI + INSTI	10 (9.6%)
2 NRTIs + bPI	29 (27.9%)
2 NRTIs + NNRTI	35 (33.7%)

DT: dual therapy; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; bPI: ritonavir boosted protease inhibitor; INSTI: integrase strand transfer inhibitor; ANTCCR5: CCR5 antagonist.

Table 3 Virologic outcomes at 24 and 48 weeks in HIV-infected patients under dual therapy with a generic fixed dose combination of DRV/r + RAL in Argentina (2014-2018). Switch and virologic groups are compared

Variable	Overall	Switch group	Virologic group	p-value
Viral load at 24 weeks (n =116)				
<50	110 (94.8%)	67 (99%)	43 (90%)	0.08
>200	6 (5.2%)	1 (1%)	5 (10%)	
Viral load at 48 weeks (n =112)				
<50	103 (91.96%)	63 (97%)	40 (85%)	0.054
50-200	2 (1.79%)	0 (0%)	2 (4%)	
>200	7 (6.25%)	2 (3%)	5(11%)	

Considering efficacy, overall high rates of virologic suppression were observed in both groups, with a trend to higher suppression rates in the SG at 48 weeks. This difference may be potentially attributable to more frequency of adherence issues, higher burden of drug resistance in the VG, and to the fact that no patient in this group had virologic suppression prior to DT initiation. Of note, in addition to comorbid conditions, patients in SG had also history of virologic failure that didn´t impact sustaining virologic suppression with this DT strategy. Prevalence of adverse events and tolerance issues leading to discontinuation of this two-drug combination was null, providing empirical evidence of the safety of this strategy in complex populations.

Our results are consistent with other studies concerning the efficacy and tolerability of DRV/r + RAL in treatment-experienced patients. Maddeadu et al, described an overall 9% probability of virologic failure at 24 months in experienced patients switched to RAL + DRV/r in the ICONA Foundation Study [16]. Jablonowska et al, in a cohort of 109 experienced patients described no discontinuations of this DT due to virologic failure, and low rates of adverse events, being simplification strategies the main reason for stopping this regimen [17,18]. Nishijima et al, on behalf of the SPARE study team, described 100% suppression rates at week 48 in patients switched to this DT due to prevention of TDF renal toxicity [19].

Despite our study has limitations inherent to its retrospective and descriptive nature that may limit the generalization of the results, our cohort provides evidence of the efficacy and safety of a generic FDC of DRV/r + RAL in a pretreated population, supporting this DT as an option for selected individuals with comorbid conditions or drug resistance.

ACKNOWLEDGEMENTS

Data in this paper were presented in part at the 17th European AIDS Conference (EACS 2019) November 6-9, 2019, Basel, Switzerland (abstract PE 2/27).

The authors would like to thank Claudia Vecchio MD, for her contribution to this project.

FUNDING

None to declare.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/069.2020

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Absceso cerebral por *Nocardia* en paciente diagnosticado de proteinosis alveolar

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Article history
Received: 7 July 2020; Revision Requested: 8 September 2020; Revision Received: 22 October 2020; Accepted: 23 October 2020; Published: 23 November 2020

Sr. Editor: La proteinosis alveolar es un raro síndrome que se caracteriza por la acumulación de surfactante y fosfolípidos en el espacio alveolar asociado a disfunción de los macrófagos. Sus manifestaciones pueden incluir desde la ausencia de clínica hasta disnea progresiva, insuficiencia respiratoria, infecciones y fibrosis pulmonar secundaria.

Se puede clasificar en primaria, por una disrupción en la señalización del factor estimulante de colonias de granulocito-macrófagos (autoanticuerpos) o hereditaria (mutaciones en CSF2RA o CSF2RB, envueltos en la producción del surfactante); y secundaria, por diversas condiciones (trastornos hematológicos, infecciones o a exposición a diversas sustancias ambientales) [1].

En todas sus formas, el sustrato fisiopatológico reside en el acúmulo de surfactante en los espacios alveolares debido a una deficiente actividad de procesamiento de éste por parte de los macrófagos, bien sea por neutralización adquirida, bien por disfunción congénita del factor estimulante de colonias de granulocitos y macrófagos (GM-CSF), por mutaciones genéticas de su receptor en la superficie celular o bien, en algunos casos, por alteraciones proteicas del propio surfactante [2].

Tiene una prevalencia de unos 7 casos por millón de habitantes y una incidencia estimada de 0,2-0,4 casos por millón de personas/año sin predominio de raza ni sexo. Es más prevalente en fumadores [3].

La proteinosis autoinmune supone más del 90 % de los casos. El tratamiento tiene como objetivo mejorar los síntomas y la calidad de vida. El lavado alveolar elimina el exceso de surfactante. Nuevas terapias basadas en la modulación autoinmune y el complejo granulocito macrófago como diana terapéutica están en investigación.

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La conjunción de una clínica e imágenes radiológicas clásicas junto con positividad en ácido periódico schiff (PAS) del material de lavado alveolar, hacen posible el diagnóstico sin confirmación mediante biopsia [2].

La nocardiosis es una infección causada por la especie oportunista *Nocardia* que se desarrolla normalmente en pacientes inmunocomprometidos. Las especies de *Nocardia* son unos actinomicetos grampositivos aerobios que se encuentran habitualmente en el suelo. Más de un centenar de especies se han descrito, pero sólo una pequeña proporción causan infecciones en el humano. Habitualmente comienza como una infección subaguda que tiende a diseminarse. La infección suele adquirirse por inhalación [4].

Nocardia es la causante de sólo el 2% de los abscesos cerebrales. Se le atribuye normalmenteuna diseminación hematógena desde un foco pulmonar o una herida contaminada [5]. Puede presentarse como meningitis o abscesificada. Se considera una enfermedad severa que presenta una mortalidad global de hasta el 20% [6]. La especie *Nocardia. farcinica* con frecuencia infecta pulmones, cerebro y piel.

Presentamos el caso de un paciente diagnosticado de proteinosis alveolar que desarrolla un absceso cerebral por *N. farcinica* al cabo de 6 meses tras el diagnóstico del proceso pulmonar. Se trata de un paciente de 49 años ex fumador (60 paquetes-año) y trabajador agrícola que ingresó por primera vez en neumología por episodio de disnea de esfuerzo. Tenía contacto habitual con un agapornis y gallinas. Había trabajado en albañilería y en agricultura. En la tomografía computerizada de alta resolución de tórax se apreció patrón pulmonar en empedrado, con áreas extensas en vidrio deslustrado con engrosamiento septal, panlobar, con respeto de algunas áreas subpleurales (Figura 1A). En la biopsia transbronquial se observaron células bronquiales e histiocitos con citoplasma espumoso, compatible con proteinosis alveolar. Reingresó a los 10 días por empeoramiento de la disnea en UCI y se diagnosticó de imagen abscesificada en lóbulo inferior izquierdo. Recibió

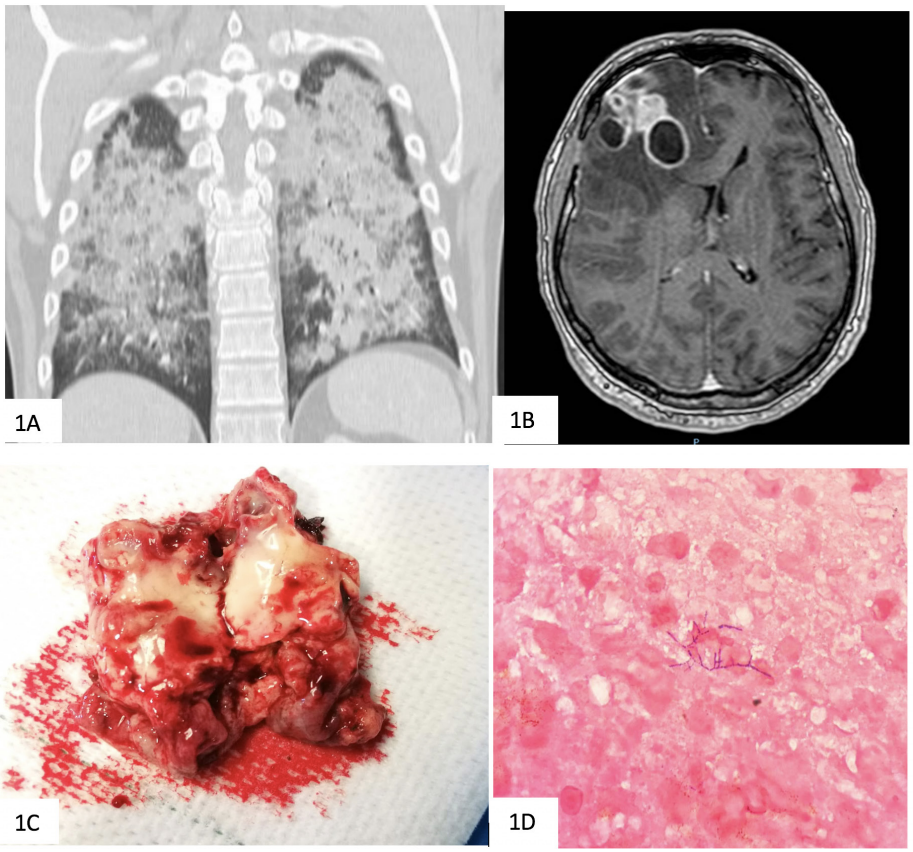

Figura 1 **1A. Tomografía computerizada de tórax con áreas extensas en vidrio deslustrado y marcado engrosamiento de los septos interlobulillares. Condensación en lóbulo inferior izquierdo. 1B. Resonancia magnética craneal con voluminoso absceso multilobulado con edema circundante. 1C. Pieza quirúrgica. Nótese el aspecto sólido-quístico y las gruesas paredes del absceso. 1D. Aspecto microscópico. Presencia de numerosos fibroblastos reactivos, neutrófilos polimorfonucleares y necrosis. Estructuras bacilares filamentosas que tiñen con plata compatibles con *Nocardia*.**

antibioterapia con piperacilina-tazobactam 4g–cada 6 horas y ciprofloxacino 500mg cada 12h seguido de linezolid 600mg cada 12h, trimetoprim (TMP) +sulfametoxazol (SMX) 160/800 mg cada 12 horas y anfotericina B 1mg / kg/día. No se aisló microorganismo responsable y la evolución fue muy favorable completando tres semanas de combinaciones antibióticas incluyendo TMP/SMX. Se benefició tras este proceso de lavado alveolar total seguido de tratamiento con factores estimulantes de granulocitos durante 4 meses. El paciente evolucionó en todo momento muy favorablemente sin disnea y fue dada de alta a domicilio con oxígeno nocturno.

Cinco meses tras este episodio consulta por cefalea inhabitual que no cede con analgesia. Se diagnosticó mediante resonancia magnética nuclear de lesión compatible con absceso cerebral con intenso edema circundante (Figura 1B). No presentaba ninguna sintomatología respiratoria ni fiebre. Tras un extenso estudio que incluyó punción lumbar, con cultivos negativos, inició terapia empírica con ceftriaxona 2g cada 12h y vancomicina 1g cada 12h. Fue intervenido resecando cuatro abscesos interconectados de paredes gruesas y contenido purulento, bien delimitado (Figura 1C). En cultivos creció *N. farcicina* (Figura 1D). identificada mediante espectrometría de masas según técnica MALDI-TOF, siendo resistente a ceftriaxona con una concentración mínima inhibitoria (CMI) de 12 mg/L y sensible a ciprofloxacino, amikacina y TMP/SMX con CMI de 0,75, 0,75 y 0,047mg/L, respectivamente. Completó antibioterapia intravenosa dirigida durante 6 semanas, seguida del mismo esquema oral (TMP/SMX 160/800mg cada 12h) durante un año con control hematológico. La evolución clínica fue muy favorable sin secuelas neurológicas y con estabilidad respiratoria.

Según nuestra revisión existen diez casos publicados de pacientes afectos de proteinosis alveolar que desarro-

llan absceso cerebral por este microorganismo, una alta proporción de ellos sin previo conocimiento del síndrome pulmonar y sin síntomas infecciosos. Aquellos con mejor evolución fueron sometidos a cirugía y esquemas antibióticos que incluían en la mayoría de los casos sulfamidas, encontrando tasas de mortalidad de hasta 80% en los casos más antiguos [7,8].

La terapia empírica para la nocardiosis es TMP/SMX, parenteral inicialmente, en dosis de 15 mg/kg TMP y 75 mg/kg SMX cada 12 horas y aminoglucósidos, excepto amikacina. La duración habitual de la terapia secuencial son 6 meses aunque los pacientes inmunocomprometidos necesitan 12 meses de tratamiento. Según publicaciones previas mantendría su eficacia aun mostrando resistencias *in vitro* [9].

La infección del sistema nervioso central por *Nocardia* es una situación rara que se ha descrito con mayor frecuencia en los últimos años debido a mejoras en su diagnóstico en pacientes inmunodeprimidos. El antecedente de proteinosis alveolar puede alertarnos sobre este microorganismo. La resistencia natural a algunos antibióticos, incluidos las cefalosporinas de tercera generación utilizadas habitualmente para infecciones del sistema nervioso central, son la clave a tener en cuenta cuando nos enfrentamos a un posible caso [10].

FINANCIACIÓN

Los autores declaran que no han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Official journal of the Spanish Society of Chemotherapy

Letter to the Editor

Revista Española de Quimioterapia
doi:10.37201/req/070.2020

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Tuberculosis cases presenting with spontaneous hemopneumothorax and hypotension

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Article history
Received: 8 June 2020; Revision Requested: 21 September 2020; Revision Received: 21 October 2020; Accepted: 5 November 2020; Published: 2 January 2021

Sir,

Tuberculosis (TB) is the second most common fatal infectious disease, following human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), in the adult population. Socio-economic deprivation, immigration, wars, omission of tuberculosis control programs, and HIV/AIDS epidemics have led to an increase in the incidence of tuberculosis. The World Health Organization (WHO) publishes a global tuberculosis report annually. The 2013 report stated that, in 2012, 8.6 million people developed TB, and 1.3 million people died from the disease, including 320,000 deaths among HIV-positive individuals [1].

As a rare complication of spontaneous pneumothorax, spontaneous hemopneumothorax (SHP) is an emergency condition that can be life threatening because of active bleeding in the pleural space; the condition has a high mortality rate and requires early diagnosis and treatment [2, 3]. A report has suggested that TB will not cause SHP due to thick and extensive pleural adhesions [4].

We present here four cases with SHP secondary to a hypovolemic shock condition due to hemorrhage, together with a literature review due to the rarity of this condition and discuss applicable treatment approaches. Pleural biopsy specimens were stained with Kinyoun and cultivated on Löwenstein–Jensen medium. Cultivation was also performed using a liquid automatized Bactec 460 TB system (Becton-Dickinson).

The first patient was a 34-year-old male admitted to the Emergency Room (ER) because of pain in his right chest and back. With no history of trauma, the patient's physical examination showed diminished breath sounds in the right hemithorax. His chest X-ray revealed an appearance consistent with hydrothorax with a partial pneumothorax line on the right (Figure 1A). Laboratory findings reported the hemoglobin level of 10.4 g/dL and a hematocrit level of 31.4%. No pathological data was detected in coagulation parameters. Tube thoracostomy (TT) was performed on the right after a preliminary diagnosis of SHP and obtained 1000 cc of fresh blood. Emergency right thoracotomy was performed following 300 ml of hemorrhage during the first hour, a clinical condition associated with hypotensive and hypovolemic shock (80/50 mmHg); a hemoglobin value reduced to 8.5 g/dL and a hematocrit value to 25.2% in the clinical follow up. Exploration showed that the apex of the upper lobe was adherent to the chest wall with a small adhesion, and aberrant vessels with diameters of ~0.4 mm at this site and an actively bleeding varicose pattern between the chest wall and pleura were identified. A suture procedure was carried out, and three units of blood were transfused. TB treatment was initiated two months after the diagnosis by histopathological and microbiological examinations of pleural biopsy specimens during emergent thoracotomy procedure.

The second patient was a 25-year-old male admitted to the ER with complaints of shortness of breath and sudden pain in the right chest showed diminished breath sounds on the right in chest auscultation. His chest X-ray showed a partial pneumothorax line on the right consistent with hydrothorax (Figure 1B). The patient had no history of trauma. Laboratory findings reported a hemoglobin level of 12.6 g/dL, and a hematocrit level of 36.8%. TT was performed on the right after a preliminary diagnosis of SHP. Air drainage was initially performed and yielded 700 cc of hemorrhagic fluid. Emergency right thoracotomy was performed following 300 ml of hemorrhage during the first hour followed by 200 ml of hemorrhage per hour, a clinical condition associated with hypovolemic hypotension (90/50 mmHg) with a hemoglobin value of 9.4 g/dL and a hematocrit value of 28.2% in his clinical follow up. Exploration found a cavity lesion with a dimension of 4×3×2

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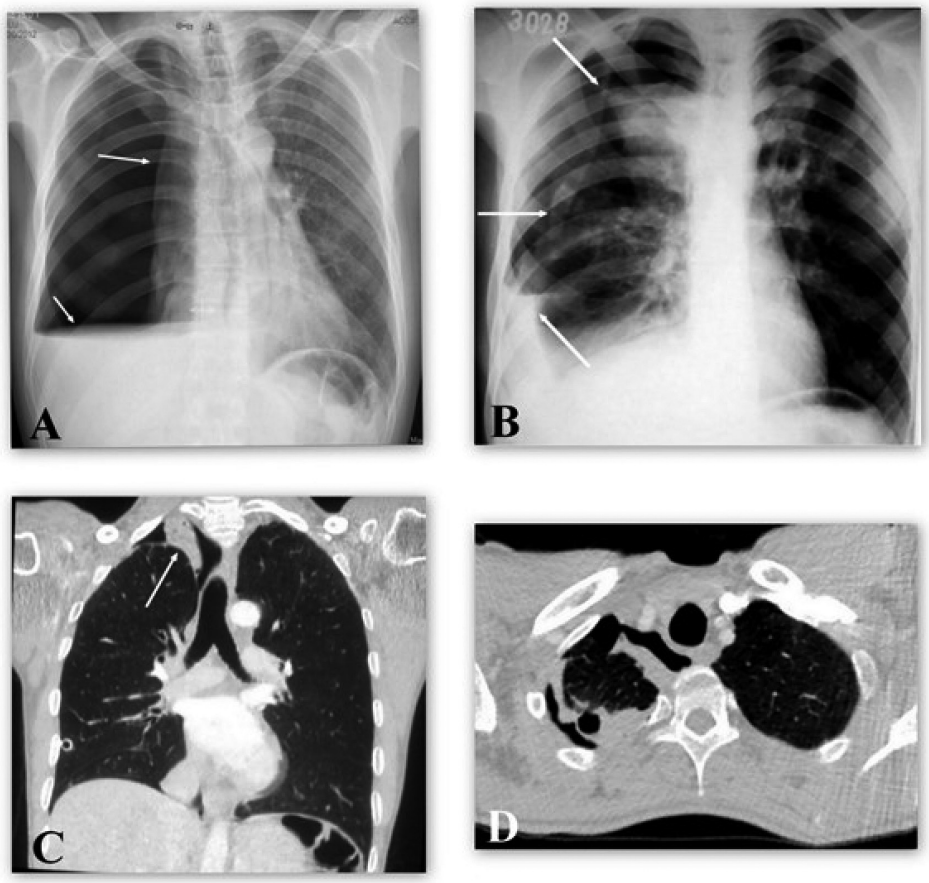

Figure 1 | **The chest X-ray and CT images of the patients**

cm, ruptured to the pleura in the apical segment of the upper lobe, and segmentectomy was performed. Clinical sample revealed acid fast bacilli (AFB). TB treatment was initiated due to this result by the Chest Diseases Department (CDD) and microbiological evaluation reported tuberculosis after two months.

The third patient was a 28-year-old male admitted to the ER with complaints of pain in the left chest and shortness of breath. With no history of trauma, the patient's thoracic radiograph showed an increased density varying with partial pneumothorax on the left. The bleeding profile and biochemical values were within normal limits and a hemoglobin level of 11.5 g/dL, and a hematocrit level of 32.4%. TT was performed on the left hemithorax. Air drainage was initially performed, yielding 1250 cc of hemorrhagic fluid. Emergency video-assisted thoracoscopic surgery (VATS) was performed in the left hemithorax following 250 ml of hemorrhagic fluid drainage during the first hour due to hypotensive and hypovolemic condition (90/40 mmHg), and a hemoglobin value reduced to 9.1 g/dL and a hematocrit to 27.2%. Exploration found bullous lesions, with a maximum diameter 2×2 cm, in the apical segment of the upper lobe and an actively bleeding adhesion lesion in the apical region of the hemithorax. The bullous lesions were excised, and bridging ligation was performed. The patient was followed up by the CDD upon detection of AFB in his sputum and treatment was initiated thereafter.

The fourth patient was a 43-year-old male with no history of trauma who was admitted to the ER because of breath difficulty and sudden pain in the right chest. He was hypotensive (90/50 mmHg), dyspneic, and tachypneic, with no breath sounds heard in the right hemithorax. His chest radiography was consistent with total pneumothorax in the right and hydrothorax and deletion of the diaphragm contours. The bleeding profile and biochemical values were within normal limits, a hemoglobin level of 9.1 g/dL, a hematocrit level of 29.4%, and a platelet count of 435,000/mm^3. TT was performed on the right hemithorax. Intravenous fluid replacement was initiated. Air drainage was initially performed, yielding 1200 cc of fresh blood. Air discharge and hemorrhagic fluid drainage were stopped at the first hour, and no additional surgical interventions were considered due to his hypotensive condition and improved dyspnea. Two units of blood were transfused upon the decrease of the hemoglobin value to 8.3 g/dL and hemat-

ocrit to 26.4%. The patient was followed up by the CDD upon detection of AFB in his sputum and a high level of adenosine deaminase (ADA: 120 U/L) in the pleural fluid; TB treatment was initiated by the CDD (Figure 1C and 1D).

Although hemopneumothorax is typically a result of trauma, SHP is not associated with a trauma history. Associated with pneumothorax, SHP involves ≥400-ml bleeding in the pleural cavity [4]. SHP is observed mostly in the adolescent age group and may cause life-threatening bleeding [2]. The incidence of SHP varies between 0.5% and 12% [5]. Our clinic treated 184 spontaneous pneumothorax patients between 2008 and 2013, only six of whom (3.2%) were diagnosed with SHP. SHP secondary to TB was found in four patients.

Three bleeding mechanisms were defined in SHP: first, the lysis of adhesions between visceral and parietal pleura; second, the rupture of congenital aberrant vessels between the parietal pleura and bulla; third, the rupture of the vascularized bullae. Some patients were found to have abnormal vascularization between the lung and parietal pleura [3]. TB, like other chronic infections, can cause abnormal vascularization connecting the parietal pleura and chest wall, leading to aneurysms and intrathoracic hemorrhage if the vessels rupture. This appears to be the explanation for the massive bleeding in two of the cases (Cases 1 and 3). Soo-Kim et al. reported their 12-year experience with SHP [4]. They showed that pleural adhesions after TB do not cause SHP because they are thick and extensive. In two of our cases, very little thickening was observed in the pleura, which could be easily decorticated, whereas SHP was caused by cavity perforation in one of our patients.

SHP cannot compensate for even minimal bleeding because the lung is collapsed, which can lead to severe blood loss. Tube thoracostomy should be the first choice in the treatment of SHP. Studies have demonstrated that only tube thoracostomy with conservative treatment is enough for the treatment of SHP in some patients [3]. Fluid and blood replacement, where necessary, should be started aimed at the stabilization of hemodynamics, the patient should be closely followed, and the need for emergency surgical intervention should be considered [6]. Persistent hemothorax ≥200 mL/h for consecutive 3 hours, persistent air leak, impaired lung expansion, and empyema are indications for thoracotomy or VATS [7].

FUNDING

None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest

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Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/078.2020

Serratia marcescens como causa de endoftalmitis tardía

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Article history
Received: 22 July 2020; Revision Requested: 1 September 2020; Revision Received: 22 September 2020; Accepted: 6 October 2020; Published: 3 December 2020

Sr. Editor: la endoftalmitis es una emergencia médica y quirúrgica dado que el pronóstico visual depende directamente del inicio temprano del tratamiento. La mayoría de los casos se producen después de la cirugía intraocular o de un traumatismo penetrante ocular.

Presentamos el caso de una mujer de 84 años con cataratas y glaucoma de ángulo abierto a la que se le realiza una cirugía conjunta de facoemulsificación con implantación de una lente intraocular (LIO) y de esclerectomía profunda no perforante en ojo izquierdo. Durante la cirugía se utilizó mitomicina C (se utilizó una dosis de 0,2 mg/ml durante 2 minutos por encima del tapete escleral superficial de la trabeculectomía) y se administró una dosis de 1 mg de cefuroxima intracamerular como profilaxis antibiótica. Al alta se pautó colirio de tobramicina y corticoides que mantuvo los 6 meses siguientes.

A los seis meses de la cirugía la paciente acude a Urgencias por pérdida de la agudeza visual y dolor en ojo izquierdo. A la exploración presentaba erosión y absceso corneal nasal con punto corneal flojo que le rozaba (nylon, material sintético no absorbible e hidrófilo, que al hidratarse pierde fuerza tensil y se fracciona a los 2-3 años) se extrae y se aplica Betadine® diluido al 5%. Presenta también ausencia de percepción de luz, hipopion e hiperemia conjuntival y se obtiene muestra conjuntival. Posteriormente se realizó vitrectomía izquierda, obteniéndose muestras de humor vítreo y acuoso para cultivo microbiológico. Como tratamiento se realizó inyección intravítrea (1 mg y 2 mg de vancomicina y ceftazidima al 0,1 ml respectivamente) y colirios reforzados de vancomicina y ceftazidima (5%, 50 mg/ml), así como vancomicina y ceftazidima intravenosa (1 g cada 12 h y 1 g cada 8 h respectivamente durante 14 días).

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En el cultivo enriquecido (agar chocolate) de conjuntiva y de los humores creció *Serratia marcescens* (sensible a gentamicina, ceftazidima y ciprofloxacino); por lo que se cambió de vancomicina a ciprofloxacino intravenoso (200 mg cada 8 h hasta completar 14 días), así como a colirio de moxifloxacino y pomada de ciprofloxacino. A pesar del tratamiento (Imagen 1), el absceso adelgazó la córnea, exponiéndose la lente intraocular y evolucionó a ptisis bulbi (atrofia del globo ocular). Dado el mal pronóstico visual, al no recuperar la percepción de luz y el desarrollo de ptisis bulbi, se decidió evisceración.

La importancia de un adecuado cuidado de las suturas viene señalada por diversos estudios en los que observan la aparición de endoftalmitis tardía con cultivo positivo a diferentes microorganismos (entre ellos también a *Serratia marcescenes*) a partir de los puntos de la sutura corneal tras facoemulsificación y lente intraocular (LIO) en este caso [1,2]. Postergar la eliminación de la sutura podría asociarse a un mayor porcentaje de dehiscencia de la sutura y, por tanto, en el desarrollo de endoftalmitis. Otros estudios señalan la posibilidad de aparición de biofilms entre las suturas y zonas inflamadas o infectadas del ojo [3].

La aparición de la endoftalmitis tras una intervención quirúrgica puede variar de 1 día a 10 años [4]. Habitualmente el pronóstico visual es malo obligando a realizar con frecuencia enucleación del ojo afecto [4,5]. En nuestro caso el mal pronóstico se acrecentó debido a que *S. marcescens* produce una proteasa citotóxica capaz de causar necrosis licuefactiva y perforación corneal [6]. En nuestro caso el microorganismo se adhirió al absceso corneal, pero en otros puede llegar a hacerlo a la LIO teniendo que extraer dicha lente para evitar una diseminación posterior.

Jampel et al. señalan que el uso de mitomicina C, una fuga de la herida, el uso de antibióticos después de la cirugía de forma intermitente o contínua pueden tener una fuerte asociación de riesgo de desarrollar endoftalmitis tras cirugía de glaucoma [7]. La identificación de estos y otros posibles factores de

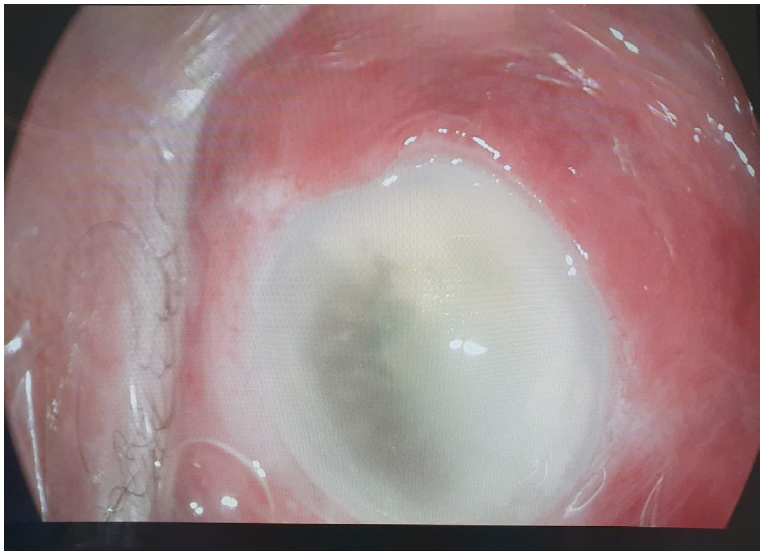

Figura 1 | **Rápida progresión de la endoftalmitis en pocos días a pesar de tratamiento antibiótico intravítreo. La imagen corresponde al segundo día de ingreso de la paciente en el servicio de oftalmología. En la imagen vemos atrofia del globo ocular (ptisis bulbi) por absceso que adelgazó la córnea. Además de hipopion y abundante fibrina intracamerular.**

riesgo como glaucoma juvenil, suturas conjuntivales con seda o el uso de corticoides sistémicos permite predecir y evitar que se produzca la infección. El uso de mitomicina C durante la cirugía de glaucoma permite reducir la fibrosis postquirúrgica y formar una ampolla de filtración duradera y efectiva para reducir la presión intraocular, a la vez de servir de puerta de entrada de microorganismos y facilitando el desarrollo de endoftalmitis tardía [8]. Otro factor de riesgo descrito que parece favorecerlo es el uso de corticoides tópicos que nuestra paciente recibió durante 6 meses.[9] El empleo de cefuroxima intracamerular al final de la cirugía de catarata ha demostrado (nivel de evidencia 1b, grado de recomendación A) reducir el riesgo de endoftalmitis aguda, aunque en nuestro caso dado que es una endoftalmitis tardía por un microorganismo con resistencia natural a la cefuroxima no parece relevante [9].

S. marcescens aunque no es un patógeno habitual del globo ocular, en caso de infección es importante realizar un diagnóstico y tratamiento temprano ya que evoluciona rápidamente hacia complicaciones fatales que implican la pérdida de visión o del globo ocular. Como medidas de prevención es fundamental una correcta hidratación de la córnea, una adecuada desinfección de las suturas sin postergar su retirada (recomendada a las 6 semanas), moderar el tiempo de uso de los corticoides a lo estrictamente necesario y, en definitiva, realizar siempre una exhaustiva vigilancia y control de estos pacientes tras la cirugía para actuar cuanto antes en caso de encontrar signos de infección o inflamación.

AGRADECIMIENTOS

A los servicios de microbiología y parasitología clínica y de oftalmología del Hospital Universitario de Basurto.

FINANCIACION

Los autores declaran que no han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Official journal of the Spanish Society of Chemotherapy

Carta al Director

Revista Española de Quimioterapia
doi:10.37201/req/095.2020

Endocarditis infecciosa por *Kytococcus schroeteri*, a propósito de dos casos clínicos

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Article history
Received: 13 August 2020; Revision Requested: 2 September 2020; Revision Received: 28 September 2020; Accepted: 13 October 2020; Published: 18 December 2020

Sr. Editor: *Kytococcus schroeteri* es una causa poco frecuente de endocarditis infecciosa (EI) sobre válvula protésica y puede ser poco reconocida debido a su similitud con otros micrococos [1,4]. La identificación de este grupo de organismos es compleja mediante pruebas bioquímicas convencionales, precisando métodos moleculares para identificarlos; de lo contrario, pueden descartarse con facilidad como contaminantes de la piel y mucosas [1,4].

Presentamos dos casos de endocarditis infecciosa por *K. schroeteri*. Se trata de un varón de 60 años, que como antecedente principal es portador de una prótesis mecánica por estenosis aórtica severa desde mayo de 2019. En octubre de 2019 acude a consulta de seguimiento presentando fiebre de hasta 38,5ºC con tiritona diaria y disnea de moderados esfuerzos de una semana de evolución. Como único antecedente epidemiológico refiere contacto con un niño sano de 6 años de edad. En consulta se realiza ecocardiograma transtorácico (ETT) con hallazgo de vegetación periprotésica que protruye el tracto de salida del ventrículo izquierdo y un absceso en la unión mitroaórtica. En la analítica sanguínea presenta una PCR de 58,8 mg/L sin leucocitosis ni neutrofilia. Ante sospecha de endocarditis infecciosa precoz sobre válvula protésica se extraen hemocultivos y se le ingresa. Se revisan las imágenes del ETT, pudiendo corresponder las mismas a un posible acúmulo cálcico, por lo que se realiza ecocardiograma transesofágico (ETE) programado; confirmándose el diagnóstico de EI. Se extraen nuevos hemocultivos y se inicia antibioticoterapia empírica con piperacilina-tazobactam 4g/8h y vancomicina 1g/8h; asociando al 3º día rifampicina 600mg/24h, para cubrir los patógenos más frecuentes en este tipo de infección (*Staphylococcus aureus*, estafilococos coagulasa negativos, estreptococos del grupo viridans y *Enterococcus faecalis*); y las sensibilidades de estos microorganismos en nuestro medio. Dado los hallazgos ecocardiográfico y clínica de insuficiencia cardiaca, se expone el caso en el comité de cardiología, indicando la sustitución de la prótesis mecánica, que se realiza al 10º día del ingreso. En el postoperatorio destaca como complicación un bloqueo auriculo-ventricular completo con frecuencia cardiaca en torno a 25-30lpm que precisa de la colocación de un marcapasos. A pesar de que en los hemocultivos recogidos al ingreso y a las 48h del diagnóstico se objetivó el crecimiento de *K. schroeteri*; no es hasta el aislamiento únicamente del microorganismo en las muestras obtenidas del material protésico, que se decide ajustar el tratamiento a antibiograma, suspendiendo piperacilina-tazobactam y manteniendo vancomicina 1g/8h y rifampicina 600mg/24h durante 4 semanas más.

Por otro lado, presentamos el caso de un varón de 48 años portador de un anillo mecánico de anuloplastia mitral desde diciembre de 2017 por prolapso mitral e insuficiencia mitral severa. Estando previamente bien, ingresa en enero de 2020 para estudio de febrícula vespertina sin foco, de dos meses y medio de evolución. No se encuentran hallazgos en los estudios, incluido ETE, salvo el crecimiento de *Granulicatella elegans* en uno de los frascos de hemocultivos, que se considera contaminante; por lo que es dado de alta con tratamiento sintomático. Reingresa nuevamente en mayo, por el mismo motivo. Esta vez, se objetiva una vegetación en velo posterior en un nuevo ETE; diagnosticándose de endocarditis infecciosa tardía sobre válvula protésica, que se atribuye a *Granulicatella elegans* aislada en el ingreso anterior; por lo que se comienza tratamiento con ceftriaxona 2g/24h y gentamicina 240mg/24h. Ante la persistencia de febrícula y empeoramiento analítico (PCR 47 mg/L, VSG 60mm, creatinina 1.49mg/dL y leucocitosis), se extraen nuevos hemocultivos, donde crece *K. schroeteri*. En función del antibiograma, tras 13 días de antibioterapia empírica, se sustituye tratamiento antibiótico a vancomicina 700mg/8h y rifampicina 900mg/24h, con posterior cambio a teicoplanina 800mg/24h por deterioro de la función renal. Tras mejoría

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inicial y después haber recibido 15 días de antibioterapia con ceftriaxona y gentamicina, y otras 3 semana con vancomicina/teicoplanina y rifampicina, reingresa de nuevo por reaparición de la fiebre de 38ºC y elevación de reactantes de fase aguda (PCR 28mg/L), sin leucocitosis. Ante la sospecha de fiebre medicamentosa (reacción adversa que desaparece al discontinuar el fármaco que la provoca sin dejar secuela), se decide suspender la antibioterapia con buena evolución. Se realiza nuevo ETE, con dudosa imagen de vegetación en porción posterior del anillo de valvuloplastia mitral. Por ello, se inicia tratamiento con levofloxacino 500mg/24h, con buena evolución.

En la actualidad ambos pacientes se encuentran asintomáticos y presentan buen funcionamiento valvular.

K. schroeteri es microorganismo coco grampositivo clasificado dentro de la familia de Dermatophilaceae [2,3]. Es una causa rara de endocarditis en válvulas protésicas, posiblemente por desconocimiento microbiológico y/o clínico [2], habiéndose documentado en la literatura un total de 7 casos previos a los nuestros [2]. Fue descubierto por primera vez en 1995 y 8 años más tarde se diagnosticó como causante de la primera endocarditis [2].

El hábitat natural de este microorganismo es desconocido, por lo tanto, también lo es su mecanismo de contaminación [2]. En los pocos casos reportados de endocarditis por Kytococcus se desconoce la causa de la bacteriemia que ha provocado la endocarditis, aunque se divaga sobre posible foco hematógeno o contaminación perioperatoria [1,2,3].

No son válidas las pruebas microbiológicas habituales para la detección de estas bacterias, precisándose métodos moleculares para su identificación, siendo la secuenciación del 16S rRNA la herramienta de diagnostico principal [2]. El avance en estas técnicas ha puesto en manifiesto la patogenicidad del microorganismo. Es por ello que su importancia en los próximos años irá en aumento, ya que se considera un importante patógeno que está aún por emerger [2].

Actualmente, en nuestro centro, se utilizan métodos basados en espectrometría de masas como es el MALDI-Tof que nos permite la identificación de colonias específicas. Otro de los avances que se está incluyendo progresivamente, es la TAAN sobre muestra de tejidos obtenidos mediante cirugía; lo que nos ha permitido acortar el tiempo hasta la identificación de microorganismo. Sin embargo, por el momento no son técnicas que se realizan de rutina en nuestro centro.

En cuanto al tratamiento, es una especie resistente a la penicilina, cefalosporina y macrólidos; con resistencia variable a quinolonas [1,4]. Se recomienda el uso de rifampicina, gentamicina, vancomicina, teicoplanina, linezolid, imipenem, tetraciclinas y daptomicina, a la que sí son sensibles [1,3,4]. Se sugieren pautas largas de antibioterapia, aproximadamente 6 semanas, aunque no hay evidencia al respecto [1,2,4].

FINANCIACIÓN

Los autores declaran que no han recibido financiación para la realización de este estudio.

CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

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